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C2C CAA CKM C1310 C1473 C1494 C200 C213 C215 C22Y C220 C221 C225 C226 C246 C25Y C250 C251 C253 C28X C280 C282 C30Y C31Y C311 C313 C338 C34Y C342 C351 C352 C355 C36Y C360 C361 C364 C366 C367 C594 C604 C62X C628 C658 C668 C697 C699 C80Y C800 C802
A5B BHA B180 B33Y B332 B42Y B420 B421 B422 B43Y B431 B433 B44Y B442 B446 B45Y B453 B48Y B480 B481 B483 B49Y B493 B53Y B530 B54Y B540 B541 B542 B543 B55Y B550 B551 B56Y B564 B565 B57Y B574 B575 B58Y B586 B59Y B596 B60Y B606 B61Y B615 B616 B64Y B640 B65Y B652 B66Y B666 B67Y B676
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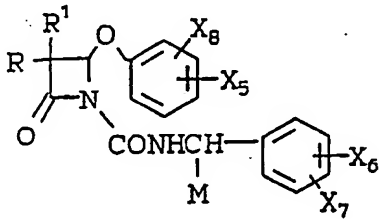
(54) Substituted azetidinones useful in the treatment of leukemia

(57) Compounds of formula I



(I)

and salts thereof, wherein R is C_{1-6}alkyl; R^1 is C_{1-6}alkyl or C_{1-6}alkoxy-C_{1-6}alkyl; and M, X_5, X_6, X_7 and X_8 are hydrogen or specific substituents, are useful in the treatment of leukemia.

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TITLE OF THE INVENTION

NEW SUBSTITUTED AZETIDINONES USEFUL IN THE TREATMENT OF CANCER

BACKGROUND OF THE INVENTION

This invention concerns the use of novel azetidinones in the treatment of certain cancers including nonlymphoblastic leukemias, acute myelogenous leukemia (FAB M1 and FAB M2), acute promyelocytic leukemia (FAB M3), acute myelomonocytic leukemia (FAB M4), acute monocytic leukemia (FAB M5), erythroleukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, chronic monocytic leukemia and conditions associated with leukemia involving activity of PMN neutral proteases e.g. disseminated intravascular coagulation. We have found that the substituted azetidinones disclosed herein are potent inhibitors of proteinase 3 (PR-3), also known as myeloblastin.

See C. Labbaye, et al., Proc. Natl. Acad. Sci. USA, vol. 88, 9253-9256, (1991), Wegner autoantigen and myeloblastin are encoded by a single mRNA; D. Campanelli, et al., J. Exp. Med., vol. 172, 1709-1714, (1990), Cloning of cDNA for proteinase 3: A serine protease, antibiotic, and autoantigen from human neutrophils; and Bories, et. al., Cell vol. 59, 959-968, (1989) Down-regulation of a serine protease, myeloblastin, causes growth arrest and differentiation of promyelocytic leukemia cells.

Recently, down regulation of PR-3 has been implicated in the proliferation and maintenance of a differentiated state of certain leukemia cells. In particular, Bories, et. al., have shown that expression of this enzyme, hereinafter designated proteinase 3/myeloblastin, can be inhibited by treatment of HL-60 human leukemia cells with an antisense oligodeoxynucleotide and that such treatment induces differentiation and inhibits proliferation of these cells. Moreover, we have now demonstrated that the treatment of the HL-60 cell human leukemia cell line, among others, with the compounds of the instant invention, likewise results in the inhibition of proliferation and induction of differentiation in such cells.

Accordingly, we believe that treatment of leukemia such as nonlymphoblastic leukemias, acute myelogenous leukemia (FAB M1 and FAB M2), acute promyelocytic leukemia (FAB M3), acute myelomonocytic leukemia (FAB M4), acute monocytic leukemia (FAB M5), erythroleukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, chronic monocytic

leukemia and conditions associated with leukemia involving activity of PMN neutral proteases e.g. disseminated intravascular coagulation, comprising: administration of a therapeutically effective amount of compound of formula I will result in remission of the disease state. Administration may be either oral or parenteral.

We have also found that a group of new substituted azetidinones are potent inhibitors of PMN elastase and PR3 and therefore are useful anti-inflammatory and antidegenerative agents.

Proteases from granulocytes and macrophages have been reported to be responsible for the acute and chronic tissue destruction associated with inflammation in diseases including rheumatoid arthritis and emphysema. Accordingly, specific and selective inhibitors of these proteases are candidates for potent anti-inflammatory agents useful in the treatment of inflammatory conditions resulting in connective tissue destruction, e.g. rheumatoid arthritis, emphysema, bronchial inflammation, chronic bronchitis, glomerulonephritis, osteoarthritis, spondylitis, lupus, psoriasis, atherosclerosis, certain pneumonias, inflammation of mucosal membranes associated with infection, sepsis, septicemia, shock, myocardial infarction, reperfusion injury, periodontitis, cystic fibrosis and acute respiratory distress syndrome.

The role of proteases from granulocytes, leukocytes or macrophages are related to a rapid series of events which occurs during the progression of an inflammatory condition:

(1) There is a rapid production of prostaglandins (PG) and related compounds synthesized

from arachidonic acid. This PG synthesis has been shown to be inhibited by aspirin-related nonsteroidal anti-inflammatory agents including indomethacin and phenylbutazone. There is some evidence that protease inhibitors prevent PG production;

(2) There is also a change in vascular permeability which causes a leakage of fluid into the inflamed site and the resulting edema is generally used as a marker for measuring the degree of inflammation. This process has been found to be induced by the proteolytic or peptide cleaving activity of proteases, especially those contained in the granulocyte, and thereby can be inhibited by various synthetic protease inhibitors, for example, N-acyl benzisothiazolones and the respective 1,1-dioxides. Morris Zimmerman et al., J. Biol. Chem., 255, 9848 (1980); and

(3) There is an appearance and/or presence of lymphoid cells, especially macrophages and polymorphonuclear leukocytes (PMN). It has been known that a variety of proteases are released from the macrophages and PMN, further indicating that the proteases do play an important role in inflammation.

In general, proteases are an important family of enzymes within the peptide bond cleaving enzymes whose members are essential to a variety of normal biological activities, such as digestion, formation and dissolution of blood clots, the formation of active forms of hormones, the immune reaction to foreign cells and organisms, etc., and in pathological conditions such as the degradation of structural proteins at the articular cartilage/pannus junction in rheumatoid arthritis etc.

PR3/myeloblastin and PMN elastase are two of these proteases. They are enzymes capable of hydrolyzing the connective tissue component elastin, a property not exhibited by the bulk of the proteases present in mammals. They act on a protein's nonterminal bonds which may be adjacent to an aliphatic amino acid. PR3 and neutrophil elastase are of particular interest because they have a broad spectrum of activity against natural connective tissue substrates. In particular, the PR3 and elastase of the granulocyte are important because, as described above, granulocytes participate in acute inflammation and in acute exacerbation of chronic forms of inflammation which characterize many clinically important inflammatory diseases.

Proteases may be inactivated by inhibitors which block the active site of the enzyme by binding tightly thereto. Naturally occurring protease inhibitors form part of the control or defense mechanisms that are crucial to the well-being of an organism. Without these control mechanisms, the proteases would destroy any protein within reach. The naturally occurring enzyme inhibitors have been shown to have appropriate configurations which allow them to bind tightly to the enzyme. This configuration is part of the reason that inhibitors bind to the enzyme so tightly (see Stroud, "A Family of Protein-Cutting Proteins" Sci. Am. July 1974, pp. 74-88). For example, one of the natural inhibitors, α_1-Antitrypsin, is a glycoprotein contained in human plasma that has a wide inhibitory spectrum covering, among other enzymes, elastases, both from the pancreas and the PMN, as well as PR3/myeloblastin.

This inhibitor is hydrolyzed by the proteases to form a stable acyl enzyme in which the active site is no longer available. Marked reduction in plasma α_1-antitrypsin activity, either genetic or due to oxidants, has been associated with pulmonary emphysema which is a disease characterized by a progressive loss of lung elasticity and resulting loss of respiratory function. It has been reported that this loss of lung elasticity is caused by the progressive, uncontrolled proteolysis or destruction of the structure of lung tissue by proteases such as elastase released from leukocytes. J. C. Powers, TIBS, 211 (1976).

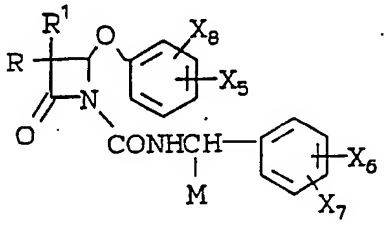
Rheumatoid arthritis is characterized by a progressive destruction of articular cartilage both on the free surface bordering the joint space and at the erosion front built up by synovial tissue invading the cartilage. This destruction process, in turn, is attributed to the protein-cutting enzyme elastase which is a neutral protease present in human granulocytes. This conclusion has been supported by the following observations:

(1) Recent histochemical investigations showed the accumulation of granulocytes at the cartilage/pannus junction in rheumatoid arthritis; and

(2) a recent investigation of mechanical behavior of cartilage in response to attack by purified elastase demonstrated the direct participation of granulocyte enzymes, especially elastase, in rheumatoid cartilage destruction. H. Menninger et al., in Biological Functions of Proteinases, H. Holzer and H. Tschesche, eds. Springer-Verlag, Berlin, Heidelberg, New York, pp. 196-206, 1979.

SUMMARY OF THE INVENTION

The present invention is directed to the treatment of leukemia, such as nonlymphoblastic leukemias, acute myelogenous leukemia (FAB M1 and FAB M2), acute promyelocytic leukemia (FAB M3), acute myelomonocytic leukemia (FAB M4), acute monocytic leukemia (FAB M5), erythroleukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, chronic monocytic leukemia and conditions associated with leukemia involving activity of PMN neutral proteases e.g. disseminated intravascular coagulation with compounds of formula I.



(I)

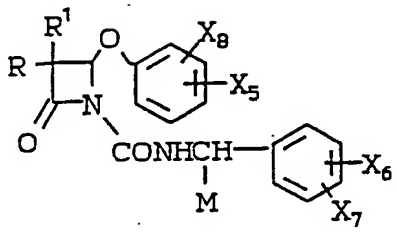
or a pharmaceutically acceptable salt thereof.

Treatment of leukemia cells comprising: administration of a therapeutically effective amount of a compound of formula I results in the inhibition of proteinase 3/myeloblastin, inhibition of elastase, inhibition of proliferation of the leukemia cells, induction of differentiation of the leukemia cells, and remission of the disease state.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment the invention concerns a method of treating leukemia comprising:

administration to a patient in need of such treatment of a therapeutically effective amount of compound of formula I



(I)

and pharmaceutically acceptable salts thereof wherein:

R is C_{1-6} alkyl;

R^1 is C_{1-6} alkyl or C_{1-6} alkoxy-C_{1-6} alkyl;

M is

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) hydroxy C_{1-6} alkyl,
(4) halo C_{1-6} alkyl,
(5) C_{2-6} alkenyl, or
(6) C_{1-6} alkoxy-C_{1-6} alkyl;

X_5 is

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo-C_{1-6} alkyl,
(4) C_{2-6} alkenyl,
(5) C_{2-6} alkynyl,
(6) carboxy,
(7) carboxy-C_{1-6} alkyl,
(8) carboxy-C_{1-6} alkylcarbonyl,
(9) carboxy-C_{1-6} alkylcarbonylamino,

(10) carboxy-C_{2-6} alkenyl,
(11) hydroxy-C_{1-6} alkyl,
(12) C_{1-6} alkylcarbonyl,
(13) C_{1-6} alkylcarbonylamino, or
(14) hydroxymethylcarbonyl C_{1-6} alkyl; and

X_6 and X_7 are each independently
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo,
(4) carboxy,
(5) C_{1-6} alkoxy,
(6) phenyl,
(7) C_{1-6} alkylcarbonyl,
(8) di-(C_{1-6}alkyl)amino,
(9) phenoxy, or

X_6 and X_7 are joined together to form the group 3,4-methylenedioxy or together with the atoms to which they are attached furan or thiophene; and

X_8 is
(a) hydrogen,
(b) C_{1-6} alkyl,
(c) halo,
(d) C_{1-6} alkoxy, or
(e) hydroxy.

In a second embodiment the invention concerns a method of inhibiting proteinase 3/myeloblastin, comprising:
administration to a patient in need of such inhibition of a therapeutically effective amount of compound of formula I or a pharmaceutically acceptable salt thereof as defined above.

In a third embodiment the invention concerns a method of inhibiting proteinase 3/myeloblastin and elastase, comprising:
administration to a patient in need of such inhibition of a therapeutically effective amount of compound of formula I or a pharmaceutically acceptable salt thereof as defined above.

In a fourth embodiment the invention concerns a method of inducing cell differentiation in leukemia cells comprising:
administration to a patient in need of such induction of a therapeutically effective amount of compound of formula I or a pharmaceutically acceptable salt thereof as defined above.

We also find that with regard to each of the above embodiments, co-administration of a compound of formula I as defined above, with an agent or agents known in the art for treatment of leukemia, including, but not limited to epsilon-aminocaproic acid, heparin, trasylol (aprotinin); prednisolone; cytosine arabinoside; b-mercaptopurine; cytarabine; an anthracycline (see Young et. al. (1981) N. Engl. J. Med. 305:139) such as dauorubicin, doxorubicin and epidoxorubicin; Vitamin A derivatives including retinoids and all-trans-retinoic acid (See Ellison R.R. et.al. (1968) Blood 32:507, Arabinosyl Cytosine: A useful agent in the treatment of leukemia in adults; Cytarabine: Therapeutic new dimensions, Semin. Oncol. 12:1 (1985, supp 3); Weinstein H.J. et. al. (1983) Blood 62:315, Chemotherapy for acute myelogenous leukemia in children and adults results in an enhanced therapeutic response.

Accordingly, in a fifth embodiment the invention concerns a pharmaceutical composition comprising:
a pharmaceutical carrier, a therapeutically effective amount of compound selected from the group consisting of epsilon-aminocaproic acid, heparin, trasylol, prednisolone, cytosine arabinoside, b-mercaptopurine, cytarabine, an anthracycline and a vitamin A derivative; and a therapeutically effective amount of compound of formula I or a pharmaceutically acceptable salt thereof as described above.

In a sixth embodiment the invention concerns a method of treating leukemia comprising:
co-administration to a patient in need of such treatment of a therepeutically effective amount of compound selected from the group consisting of epsilon-aminocaproic acid, heparin, trasylol, prednisolone, cytosine arabinoside, b-mercaptopurine, cytarabine, an anthracycline, and a vitamin A derivative; and a therapeutically effective amount of compound of formula I or a pharmaceutically acceptable salt thereof as described above.

In a seventh embodiment the invention concerns a method of inhibiting proteinase 3/myeloblastin, comprising:
co-administration to a patient in need of such inhibition of a therapeutically effective amount of compound selected from the group consisting of epsilon-aminocaproic acid, heparin, trasylol, prednisolone, cytosine arabinoside, b-mercaptopurine, cytarabine, an anthracycline, and a vitamin A derivative;and a therapeutically effective amount of

compound of formula I a pharmaceutically acceptable salt thereof as defined above.

In an eighth embodiment the invention concerns a method of inhibiting proteinase 3/myeloblastin and elastase,
comprising:.
administration to a patient in need of such inhibition of a therapeutically effective amount of compound selected from the group consisting of epsilon-aminocaproic acid, heparin, trasylol, prednisolone, cytosine arabinoside, b-mercaptopurine, cytarabine, an anthracycline, and a vitamin A derivative; and a therapeutically effective amount of compound of formula I or a pharmaceutically acceptable salt thereof as defined above.

In a ninth embodiment the invention concerns a method of inducing cell differentiation in leukemia cells comprising:
administration to a patient in need of such inducing of a therapeutically effective amount of compound selected from the group consisting of epsilon-aminocaproic acid, heparin, trasylol, prednisolone, cytosine arabinoside, b-mercaptopurine, cytarabine, an anthracycline and a vitamin A derivative; and a therapeutically effective amount of compound of formula I or a pharmaceutically acceptable salt thereof as defined above.

With regard to each of the embodiments described above, the invention concerns a first genus of compounds of formula I

wherein:

M is

(a) C_{1-6} alkyl,
(b) hydroxy C_{1-6} alkyl,
(c) halo C_{1-6} alkyl; and
(d) alkyl, and

X_5 is

(a) carboxy, or
(b) carboxy C_{1-6} alkyl.

One class of this genus concerns compounds of formula I wherein

X_5 is carboxy or carboxy-C_{1-3}alkyl;
X_8 is hydrogen, F, Cl, CH_3 or CH_2CH_3;
M is C_{1-3} alkyl or allyl; and
X_6 is hydrogen, C_{1-6} alkyl, C_{1-6}alkoxy and
X_7 is hydrogen or
X_6 and X_7 are joined together to form the group 3,4-methylenedioxy or together with the atoms to which they are attached form furan.

One subclass of this class concerns the use of compounds of Formula I wherein
R is ethyl, and
R^1 is methyl or ethyl.

Exemplifying the invention is the use of the following compounds of Formula I:

(1) (4S)-3,3-diethyl-1-[(R)-α-ethyl-benzyl-aminocarbonyl]-4-[(4-carboxymethyl)-phenoxy]azetidin-2-one;

(2) (4S)-3,3-diethyl-1-[(R)-α-n-propyl-benzylamino-carbonyl]-4-[(4-carboxymethyl)-phenoxy]azetidin-2-one;

(3) (4S)-3,3-diethyl-1-[(R)-α-allyl-(4-methyl)benzyl-aminocarbonyl]-4-[(4-carboxy-methyl)phenoxy]azetidin-2-one;

(4) (4S)-3,3-diethyl-1-[(R)-α-allyl-(3,4-methylenedioxy)-benzylaminocarbonyl]-4-[(4-carboxymethyl)phenoxy]azetidin-2-one;

(5) (4S)-3,3-diethyl-1-[(R)-α-n-propyl-(3,4-methylenedioxy)-benzylaminocarbonyl]-4-[(4-carboxymethyl)-phenoxy]azetidin-2-one;

(6) (4S)-3,3-diethyl-1-[(R)-α-n-propyl-(4-methyl)-benzylaminocarbonyl]-4-[(4-carboxy)phenoxy]azetidin-2-one; and

(7) (4S)-3,3-diethyl-1-[(R)-α-n-propyl-(4-methyl)-benzylaminocarbonyl]-4-[(4-carboxymethyl)-phenoxy]azetidin-2-one.

(8) (4S)-3,3-diethyl-1-[[(R)-1-(benzofuran-5-yl)butyl-amino]carbonyl]-4-[(4-carboxymethyl) phenoxy]azetidin-2-one.

Further exemplying this invention is the use of the following compounds of Formula I

(1) (4S)-3,3-diethyl-1-[(R)-α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4-carboxy-3-chloro) phenoxy]azetidin-2-one.

(2) (4S)-3,3-diethyl-1-[(R)-α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4-carboxy-3-fluoro) phenoxy]azetidin-2-one.

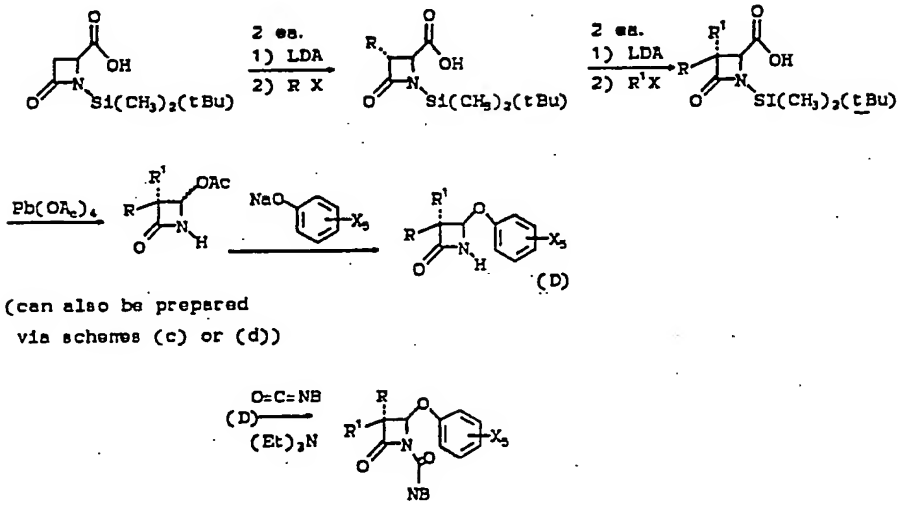
(3) (4S)-3,3-diethyl-1-[(R)-α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4-carboxy-3-methyl)-phenoxy]azetidin-2-one.

(4) (4s)-3,3-diethyl-1-[(R)-α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4-carboxy-3-methyl)-phenoxy]azetidin-2-one.

(5) (4S)-3,3-diethyl-1-[(R)-α-n-propyl-(4-ethoxy)benzylaminocarbonyl]-4-[(4- carboxymethyl) phenoxy]azetidin-2-one.

The compounds of the invention are prepared by known methods or methods depicted in the following schemes are Examples. For example, methods for making such compounds are disclosed in EP 0 337 549, published October 18, 1989, which is hereby incorporated by reference.

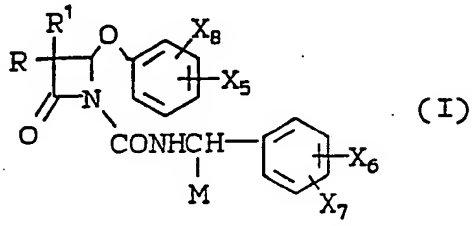
Compounds of Formula I are conveniently prepared according to the Scheme below as illustrated by Examples 20 and 21:



It has been found that the compounds of formula I, inhibit protease 3/myeloblastin as shown in Table 1.

TABLE 1

SECOND ORDER RATE CONSTANTS FOR THE INHIBITION OF HUMAN PROTEINASE 3



(I)

wherein M is n-propyl; 8 is hydrogen; and

X_5	X_6	X_7	SORC $[M^{-1}, Sec^{-1}]$
$-CH_2COOH$	4-Mc	H	27,300

ASSAY

The PR3 catalyzed hydrolysis of MeO-Succ-AAPV-pNA was measured in a spectrophotometer monitoring absorbance at 410 n,m. The enzymatic activity was determined in 45 mM TES at pH 7.5, 450 mM NaCl and 10 % DMSO. The data were fit by non-linear regression to equation 1 to obtain the initial rates. The nonlinear progress curves observed with time dependent inhibitors were fit to equation 2 to obtain the first order rate constant K_{obs}. Results were expressed as k_{obs}/I which is the second order rate constant (SORC) in per mole per second for inactivation of the enzyme.

EQN 1 $Y = v_i X + B$

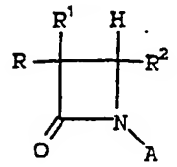
EQN 2 $Y = v_s * x + [(v_o - v_s) (1-e^{(-K_o * x)}) / K_o] + A_o$

Kinetic constants for the inhibition of PR3 catalyzed hydrolysis of 0.2 mM MoO-succ-AAPV-pNA were determined by varying the concentration of inhibitor present in the reaction vessel.

It has also been found that the compounds of Formula (I) are effective inhibitors of the proteolytic function of human neutrophil elastase as shown below in Table 2.

It has also been found that the compounds of Formula (I), are effective inhibitors of the proteolytic function of human granulocyte elastase as shown on the next page:

TABLE 2



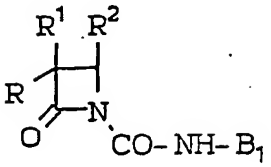
R	R^1	R^2	A	ID_{50} (mg/ml)	Ki (mM)	k_{obs}/I ($M^{-1}sec^{-1}$)
H	H	$SOCH_3$	$COCH_3$	10.00		
H	H	$OCOCH_3$	$COCH_3$	3.00		
H	C_2H_5	$OCOCH_3$	H	15.00		
H	C_2H_5	$OCOCH_3$	$COCH_3$	0.10	0.36	15100
H	n-propyl	$OCOCH_3$	$COCH_3$	0.01		
H	C_6H_5 (trans)	$COOC_2H_5$	H	10.00		
H	H	$COOCH_2C_6H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	3.00		
CH_3	CH_3	$OCOCH_3$	$COCH_3$	0.50		
H	C_6H_5 (trans)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	4.00		
H	C_6H_5 (cis)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	3.00		
H	CH_3O	$COOCH_2C_6H_5$	$COCH_3$	2.00		
H	n-propyl	$OCOCH_3$	$SO_3^-(Bu)_4N^+$	8.00		
H	C_2H_3 (cis)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.02		
H	C_2H_5 (cis)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.05		3925
H	C_2H_5 (trans)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.05		39300
H	C_2H_5 (trans)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}CH_3)$	0.01		
H	n-propyl (trans)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.06		
H	CH_3CHCH (cis)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.05		
H	CH_2CH	$p\text{-}(C_6H_4\text{-}NO_2)$	H	1.50		
H	C_2H_5	$OCOCH_2CH_2COOH$	$COCH_3$		2.00	4514
H	C_2H_5 (trans)	OCOPh	$COCH_3$		0.19	81000

TABLE 2 (Continued)

R	R^1	R^2	A	ID_{50} (mg/ml)	Ki (mM)	k_{obs}/I ($M^{-1}sec^{-1}$)
H	C_2H_5 (cis)	OCOPh	$COCH_3$		0.21	28500
H	C_2H_5	$OCOCH_3$	$COCH_2CH_2COOH$		1.43	2250
H	C_2H_5 (cis)	$OCOCH_3$	COPh		0.14	
H	C_2H_5 (trans)	$COCH_3$	COPh		0.34	76600
H	C_2H_5 (trans)	OPh	$COCH_3$		4.30	5270
H	C_2H_5 (trans)	OC_2H_5	$COCH_3$		11.90	1670
H	C_2H_5 (trans)	OPh-p-COOH	$COCH_3$		3.40	8727
H	C_2H_5 (trans)	OPh-p-COOH	$COOC_2H_5$		2.10	8680
H	C_2H_5 (trans)	OPh-p-COOH	$CONHCH_3$		16.50	
H	C_2H_5 (cis)	$CON(CH_2)_4$	$SO_2(p\text{-}C_6H_4\text{-}CH_3)$		27.70	541
H	C_2H_5 (cis)	$COOCH_2C_6H_4$-p-COOH	$SO_2(p\text{-}C_6H_4\text{-}CH_3)$		4.20	299
H	C_2H_5 (cis)	$CON(CH_3)CH_2COOH$	$SO_2(p\text{-}C_6H_4\text{-}CH_3)$		22.00	165
H	C_2H_5 (trans)	OCH_2COOH	$COOC_2H_5$			512
H	C_2H_5 (cis)	OCH_2COOH	$COOC_2H_5$			796
H	n-propyl (trans)	OCH_2COOH	$COOC_2H_5$			1504
H	C_2H_5 (trans)	$OCH_2CONHCH_2COOH$	$COOC_2H_5$			1000
H	C_2H_5 (trans)	$OCH(CH_3)COOH$	$COOC_2H_5$			346
H	C_2H_5 (cis)	$COOCH_2COOH$	$SO_2(P\text{-}C_6H_4\text{-}CH_3)$			1554

ID_{50} is the effective dosage in micrograms per milliliter (mg/ml) for 50% inhibition of the enzyme activity two minutes after time zero. Ki is the concentration of the inhibitor (micromolar, mM) giving 50% of the control enzyme activity. k_{obs}/I (M^{-1} sec^{-1}) is the second order rate constant of inactivation of the enzyme.

TABLE 3



R	R^1	R^2	B_1	k_{obs}/I
C_3H_7	CH_3	O-(4-COOH-Ph)	CH_2Ph	1900
C_2H_5	CH_3	O-(4-COOH-Ph)	$CH(CH_3)Ph$	15,000
C_3H_7	H	O-(4-COOH-Ph)	CH_2Ph	5,000
C_2H_5	C_2H_5	O-(4-$CO(CH_2)_2$COOH-Ph)	CH_2(4-Ph-Ph)	107,045
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2(4-Ph-Ph)	37,000
C_2H_5	CH_2OCH_3	O-(4-COOH-Ph)	CH_2(4-Ph-Ph)	44,533
C_2H_5	C_2H_5	O-(4-NO_2-Ph)	CH_2Ph	6,847
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2 (2-Anthracene)	36,177
C_2H_5	C_2H_5	O-(2-CH_2OH-Ph)	CH_2Ph	2961
C_2H_5	C_2H_5	O-(4-CH_2COOH-Ph)	CH_2Ph	3175
C_2H_5	C_2H_5	O-(4-$CH_2CH(NH_3^+)$-Ph) CO_2^-	CH_2Ph	2540
C_2H_5	C_2H_5	O-(4-$NHCOCH_3$-Ph)	CH_2Ph	3503
C_2H_5	C_2H_5	O-(4-$NHCOCH_2CH_2$COOH-Ph)	CH_2Ph	2568
C_2H_5	C_2H_5	O-(4-CH_3CO-Ph)	CH_2-(4-COOH-Ph)	2807
C_2H_5	C_2H_5	O-(4-CH_3CO-Ph)	CH_2(4-CH_3CO-Ph)	5916
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(2-furyl)	5223
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(2-thienyl)	4925
C_2H_5	C_2H_5	O-(4-COOH-Ph)	n-C_9H_{19}	8300
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$(CH_2)_3Ph$	4537
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2Naph	21,269

TABLE 3 (CONTINUED)

R	R^1	R^2	B_1	k_{obs}/I
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$(CH_2)_4Ph$	10,894
C_2H_5	C_2H_5	O-Ph	CH_2-(4-COOH-Ph)	1501
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-cyclohexyl	1424
C_2H_5	H	O-(4-COOH-Ph)	CH_2Ph	4000
C_2H_5	CH_3	O-(4-COOH-Ph)	CH_2Ph	2000
$CH_2CH=CH_2$	H	O-(4-COOH-Ph)	CH_2Ph	5400
C_3H_7	C_2H_5	O-(4-COOH-Ph)	CH_2Ph	3280
cyclopentane (R and R^1 combined and form the cyclopentane ring)		O-(4-COOH-Ph)	CH_2Ph	1900
C_2H_5	CH_2OCH_3	O-(4-COOH-Ph)	CH_2Ph	1900
C_2H_5	CH_3	O-(4-COOH-Ph)	$CH_2CH(CH_3)Ph$	2553
C_2H_5	C_3H_7	O-(4-COOH-Ph)	CH_2-(2-Naph)	51,000
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH(CH_3)$-(1-Naph)	14,128
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(4-Cl-Ph)	3419
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH_2(4-CH_3-Ph)$	3965
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2(4-F-Ph)	2337
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH_2(4-OCH_3-Ph)$	5162
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH_2(4-NO_2-Ph)$	5075
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH(CH_3)$-(3-Cl-4-cyclohexyl-Ph)	20,776
C_2H_5	CH_2OCH_3	O-(4-COOH-Ph)	CH_2-(3,4-methylenedioxy-Ph)	16,984
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(2-benzofuran)	13,151
C_2H_5	C_2H_5	O-(2-(6-COOH-Naph))	CH_2Ph	5561
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2(4-(4-Cl-Ph)-SO_2NHCO-Ph)	1730

TABLE 3 (CONTINUED)

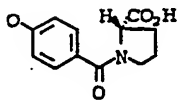
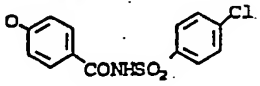
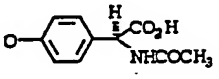
R	R^1	R^2	B_1	k_{obs}/I
C_2H_5	C_2H_5	O-(3-CO-NHCH$_2$-Ph)	CH_2Ph	3047
C_2H_5	C_2H_5	O-(3-COOH-Ph)	CH_2Ph	1763
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(4-PhO-Ph)	12,036
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(4-HN$(CH_3)_2$-Ph) $^+CF_3COO^-$	9983
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$(CH_2)_4OPh$	3447
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$(CH_2)_4CH(OH)Ph$	4200
C_2H_5	C_2H_5	O-(4-N$(CH_3)_3I^-$Ph	CH_2Ph	1700
C_2H_5	C_2H_5	-1-imidazolyl	CH_2Ph	200
C_2H_5	C_2H_5		CH_2Ph-	2000
C_2H_5	C_2H_5		CH_2Ph	6300
C_2H_5	C_2H_5		CH_2Ph	2422

TABLE 3 (Continued)

R	R^1	R^2	B_1	k_{obs}/I
C_2H_5	H	0-(4-COOH-Ph)	Ph-4-COOH	13,563
C_3H_7	C_3H_7	0-(4-COOH-Ph)	CH_2Ph	2,500
allyl	C_2H_5	0-(4-COOH-Ph)	CH_2Ph	1974
CH_2Ph	C_2H_5	0-(4-COOH-Ph)	CH_2Ph	87
C_2H_5	CH_2OCH_3	0-(4-COOH-Ph)	CH_2-2-Naph	50,000
C_2H_5	H	Ph-4-COOH	CH_2Ph	900
H	OMe	Ph-4-COOH	CH_2-2-Naph	1340
C_2H_5	C_3H_7	0-(4-COOH-Ph)	CH_2Ph-3-CF_3	55,000
C_2H_5	CH_3	0-(4-COOH-Ph)	CH(Et)-5-benzofuryl	750,000
C_2H_5	CH_3	0-(4-COOH-Ph)	CH(Et)-3-thienyl	78,800
C_2H_5	CH_2OCH_3	0-(4-COOH-Ph)	CH(nPr)Ph	75,000
C_2H_5	C_3H_7	0-(4-$CO(CH_2)_2COOH$-Ph)	CH(Et)Ph	87,000
C_2H_5	C_3H_7	0-(4-CH_2COOH-Ph)	CH(Et)Ph	54,000
C_2H_5	CH_3	0-(4-COOH-Ph)	Cyclopentyl	—
C_2H_5	CH_3	0-(4-COOH-Ph)	$CH(CH_3)CH_2CH_2CH_3$	—
C_2H_5	CH_3	0-(4-$CONH_2$Ph)	CH_2Ph	12,500
C_2H_5	CH_3	0-(4-COOH-Ph)	CH_2(3,5-diMe-4-COOH-Ph)	5,600
C_2H_5	CH_3	0-(4-$CONH_2$Ph)	CH_2(3,5-diMe-4-COOH-Ph)	30,000
C_2H_5	CH_3	0-(4-COOH-Ph)	CH_2(3,4-diMeO-Ph)	11,300

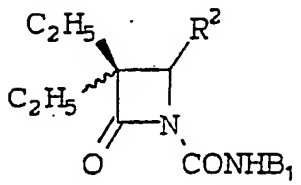
Me represents CH_3

Ph represents phenyl

Pr represents propyl

Bu represents butyl

TABLE 4

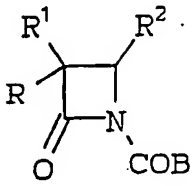


R^2	B^1	k_{obs}/I
OCH_2COOH	CH_2Ph-4-Ph	2901
O-(4-COOH-Ph)	CH_2	4157
O-(allyl)	CH_2Ph-4-Ph	12,545
-1-imidazolyl	CH_2Ph-4-Ph	461
1-triazolyl	CH_2Ph-4-Ph	2144
(1-methyl-tetrazol-5-yl)thio	CH_2Ph	3658
(1-H-triazol-3-yl)thio	CH_2Ph	116
1-tetrazolyl	CH_2Ph	948
[2H-1-pyridonyl]	CH_2Ph	357
O-Ph-4-$CONH_2$	CH_2-2-Naph(6-COOH)	40,650
1-benzimidazolyl	CH_2Ph	69
	CH_2Ph	351
O-glyceryl	CH_2Ph	818
OCH_2CONH_2	CH_2-Ph-4-Ph	51,802
NH-COOMe	CH_2Ph	496
OCH_2-COOH	CH-(Et)-Ph	5711
OCH_2-$CONH_2$	CH-(Et)-Ph	102,974
O-(4-COOH-Ph)	nBu	—
O-(4-COOH-Ph)	cyclopentyl	—
O-$CH_2CON(Et)_2$	CH(Et)Ph	—

TABLE 4 (Continued)

R^2	B_1	k_{obs}/I
O-(4-COOH-Ph)	CH_2Ph(2-OH)	1461
O-(4-COOH-Ph)	CH_2Ph(4-tBu)	21,774
O-(4-COOH-Ph)	CH_2Ph(4-(3-COOH)Ph)	14,727
O-(4-COOH-Ph)	CH_2Ph(4-CO-N O)	2036
O-(4-COOH-Ph)	CH_2Ph(4-CH_2Ph)	8032
O-(4-COOH-Ph)	CH_2Ph(3-CH_3)	6932
O-(4-COOH-Ph)	CH_2Ph(3,4-$(CH_2)_4$)	62,883
O-(4-COOH-Ph)	CH_2Ph(3,4-DiMe)	20,600
O-(4-COOH-Ph)	CH_2Ph(4-i-Pr)	18,846
O-(4-COOH-Ph	CH_2Ph(4-S(O)$_2$Me)	3350
O-(4-COOH-Ph)	CH_2Ph(4-COMe)	5916
O-(4-COOH-Ph)	CH_2Ph(4-OMe-3-Me)	13,126
O-(4-COOH-Ph)	CH_2-Ph(4-OCH_2Ph)	12,036
O-(4-CH(COOH)NHAc-Ph)	CH_2Ph	1676
O-(4-CH(OH)COOH-Ph)	CH_2Ph(3,4-DiMe)	17,626
O-(3-OH-4-COOH-Ph)	CH_2Ph(4-Me)	9252
O-(2-$(CH_2)_3NMe_2$-Ph)	CH_2Ph	629
O-(4-CH_2COOH-Ph)	CH_2Ph(4-Ph)	28,870

TABLE 5



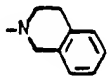
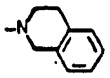
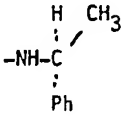
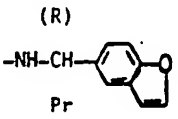
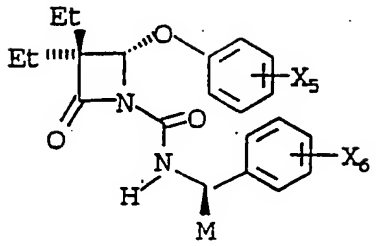
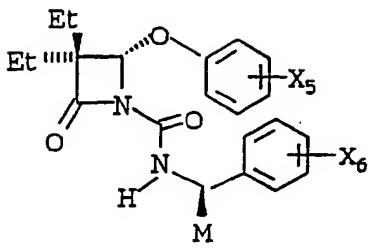
R	R^1	R^2	B	k_{obs}/I
C_2H_5	$-CH_3$	O-(4-COOH-Ph)		4376
C_2H_5	-H	O-(4-COOH-Ph)		10,066
C_3H_7	C_3H_7	O-(4-COOH-Ph)		1446 (lower R_f isomer) 4324 (higher R_f isomer)
C_2H_5	H	O-(4-COOH-Ph)	$-N(CH_2Ph)_2$	5977
C_2H_5	H	O-(4-COOH-Ph)	$-OCH_2-(4-COOC_2H_5-Ph)$	227,460
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$-OCH_2-(4-COOC_2H_5-Ph)$	14,331
C_2H_5	H	O-(4-COOH-Ph)	$-N(C_2H_5)(CH_2Ph)$	82,956
C_2H_5	C_2H_5	O-(4-CH_2COOH-Ph)		847,000

TABLE 6



X_5	M	X_6	k_{obs}/I
4-COOH	Et	H	92,000
4-COOH	CH_2OMe	H	6,094
4-CH_2COOH	Et	H	140,000
4-COOH	Me	4-Me	47,000
4-COOH	Et	4-Me	--
4-COOH	$PhCH_2$	H	25,000
4-CH_2COOH	nPr	H	227,000
4-COOH	nPr	CH_3	--
4-COOH	nPr	H	120,000
4-COOH	Et	3,4-(OCH_2O)	--
4-CH_2COOH	nBu	H	--
4-COOH	allyl	H	--

TABLE 7



X_5	M	X_6	k_{obs}/I
4-COOH	Me	H	4016
4-COOH	Me	4-Ph	74,000
4-CH_2COOH	Me	H	8,373
4-COOH	Me(s)	4-Ph	49246
4-COOH	Ph	4-Ph	67754
4-COOH	Me	4-(2'-Cl-Ph)	245130
4-COOH	Et	4-Ph	26382
4-COOH	Et	H	76204
4-CO-$(CH_2)_2$-COOH	Me	H	37084
4-CO-$(CH_2)_2$COOH	Et	H	272190
3,5-Me_2-4-COOH	Et	H	24,994
4-CH_2COOH	Et	H	126,000
3-OH-4-COOH	Et	H	124560
3-CH_2COOH	Me	H	5885
4-CH=CH-COOH	Me	H	9101
4-COOH	CH_2OMe(S)	H	6981
4-CH_2COOH	CH_2OMe(S)	H	
4-COOH	Me	4-Me	10680
4-COOH	iPr(S)	H	4743
4-COOH	iPr	H	177075
4-CH_2COOH	nPr	H	188,000
4-CH_2COOH	CH_2OMe(R)	H	11004
3,5-Me_2-4-COOH	nPr	H	

TABLE 7 (Continued)

X_5	M	X_6	k_{obs}/I
3-CH_2COOH	Et	4-Me	
4-$(CH_2)_2COQH$	Me	H	9481
3-CH_2COOH	Et	H	81018
4-COOH	CH_2OMe(R)	H	6981
4-COOH	Et	3-Me	
4-CH_2COOH	Et	3-Me	
4-$CO(CH_2)_2COOH$	allyl	4-Me	
4-COOH	Me	4-Me	
4-CH_2COOH	Et	3-Cl	
4-COOH	Et	3-Cl	
4-COOH	allyl	3-Me	
4-COOH	nPr	3-Me	
4-CH_2COOH	allyl	4-Me	664,000
3-CH_2COOH	allyl	4-Me	
4-CH_2COOH	allyl	3-Me	
4-CH_2COOH	nPr	3-Me	
4-$CO(CH_2)_2COOH$	nPr	4-Me	
3-CH_2COOH	allyl	H	
3-CH_2COOH	CH_2OMe(S)	H	
4-COOH	allyl	H	
4-CH_2COOH	allyl	H	
4-COOH	Et	4-Me	
4-COOH	Et(S)	4-Me	
4-COOH	allyl	4-Me	
4-COOH	nPr	4-Me	389,000
3-CH_2COOH	nPr	4-Me	
4-CH_2COOH	nPr	4-Me	557,000

TABLE 7 (Continued)

X_5	M	X_6	k_{obs}/I
3-CH_2COOH	Et	4-Cl	
4-COOH	Et	4-Cl	
4-CH_2COOH	Et	4-Me	
3-CH_2COOH	Et	3-Cl	
4-COOH	allyl	3,4-methylenedioxy	
4-COOH	nPr	3,4-methylenedioxy	
4-CH_2COOH	allyl	3,4-methylenedioxy	605,000
4-CH_2COOH	nPr	3,4-methylenedioxy	867,000
3-CH_2COOH	CH_2COOH	4-Me	
3-CH_2COOH	nPr	H	
4-COOH	Et	3,4-methylenedioxy	
4-CH_2COOH	Et	3,4-methylenedioxy	
4-COOH	Et	3,4-Me_2	
4-COOH	$CH_2C=CCH_3$	H	
4-CH_2COOH	$CH_2C=CCH_3$	H	
4-COOH	nBu	H	
2-NO_2-4-CH_2COOH	Et	H	
4-COOH	Et	4-F	
4-COOH	Et	3-Me-4-OMe	
3-F,4-COOH	nPr	4-Me	464,500
3-Cl,4-COOH	nPr	4-Me	621,000
3-Me,4-COOH	nPr	4-Me	186,500
3-F,4-CH_2COOH	nPr	4-Me	637,000
3-Cl,4-CH_2COOH	nPr	4-Me	589,000
3-Me,4-CH_2COOH	nPr	4-Me	998,000
4-Ch_2-(OOH)	nPr	3,4(-CH=CH-O-)	848,000

Enzyme Assays for the Inhibition of Human Polymorphonuclear Leukocyte Elastase Via Hydrolysis of N-t-Boc-alanyl-alanyl-prolylalanine-p-nitroanilide (Boc-AAPAN) or N-t-Boc-alanyl-prolylvaline-p-nitroanilide (Boc-AAPVN) Reagent:

0.05M TES (N-tris[hydroxymethyl]methyl-2-amino-ethanesulfonic acid) Buffer, pH 7.5.

0.2 mM Boc-AAPAN or Boc-AAPVN.

To prepare substrate, the solid was first dissolved in 10.0 ml DMSO. Buffer at pH 7.5 was then added to a final volume of 100 ml.

Crude extract of human polymorphonuclear leukocytes (PMN) containing elastase activity.

Inhibitors (azetidinones) to be tested dissolved in DMSO just before use.

To 1.0 ml of 0.2 mM Boc-AAPAN in a cuvette, 0.01-0.1 ml of DMSO with or without inhibitor was added. After mixing, a measurement was taken at 410 mμ to detect any spontaneous hydrolysis due to presence of test compound. 0.05 Milliliters of PMN extract was then added and the ΔOD/min at 410 mμ was measured and recorded. Beckman model 35 spectrophotometer was used.

Results in Table 2 were reported as ID_{50}, effective dosage in micrograms per milliliter (μg/ml) for 50% inhibition of the enzyme activity 2 minutes after zero time.

Results were also expressed as Ki, the micromolar concentration of the inhibitor (μM) giving 50% of the control enzyme activity; or as k_{obs}/I which is the second order rate constant in per mole per second for inactivation of the enzyme.

Accordingly, compounds of formula I are useful in the treatment of certain cancers including nonlymphoblastic leukemias, acute myelogenous leukemia (FAB M1 and FAB M2), acute promyelocytic leukemia (FAB M3), acute myelomonocytic leukemia (FAB M4), acute monocytic leukemia (FAB M5), erythroleukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, chronic monocytic leukemia and conditions associated with leukemia involving activity of PMN neutral proteases e.g. disseminated intravascular coagulation.

Similarly, compounds of formula I are useful for the inhibition of proteinase 3/myeloblastin, inhibition of elastase, inhibition of proliferation of leukemia cells, inducing differentiation of leukemia cells and remission of the disease state of leukemia.

Moreover, as described above, such treatment may optionally comprise the co-administration of an agent such as a compound selected from the group consisting of epsilon-aminocaproic acid, heparin, trasylol, prednisolone, cytosine arabinoside, b-mercaptopurine, cytarabine, an anthracycline and a vitamin A derivative.

For each of the uses, the compounds of Formula (I) and optional treatment agents, may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcataneous injections, intravenous, intramuscular, intrasternal injection or infusion

techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate. one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate, and

condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution glucose in water and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of Formula (I), and optional treatment agents may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient

which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the anti-inflammatory agents are employed.

The amount of each active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 5 mg to 2000 mg or 5000 mg of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. For purposes of this specification, this broad dosage range is specifically intended to include, but is not limited to, range of 5 mg to 2000 mg; 25 mg to 2000 mg; 5 mg to 1000 mg; 25 mg to 1000 mg; 5 mg to 500 mg; and 25 mg to 500 mg. Dosage unit forms will generally contain between from about 25 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following example illustrates the preparation of the compounds useful in the method of treatment of the present invention, but does not limit the scope of the invention.

EXAMPLE 1

1-p-nitrophenylsulfonyl-4-benzyloxycarbonyl azetidin-2-one

Diazabicycloundecane (152 mg, 1 mM) was added to a mixture of 205 mg (1 mM) 4-benzyloxycarbonyl azetidin-2-one and 181 mg (1 mM) p-nitrobenzene-sulfonyl chloride in 10 ml methylene chloride at room temperature. After stirring 2-1/2 hours, the orange solution was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 64 mg (17%) of 1-p-nitrophenylsulfonyl-4-benzyloxycarbonyl azetidin-2-one.

NMR ($CDCl_3$): δ 3.3 (2H, doublet-quartet), 4.8 (qt. 1H), 5.2 (s, 2H), 7.2 (s, 5H), 8.2 (mlt. 4H).

EXAMPLE 2

1-Acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one

Step A: Preparation of 2-methyl-prop-1-enylacetate

A mixture of 72 g (1 M) isobutyraldehyde, 153 g (1.5 M) acetic anhydride and 12 g (0.125 M) potassium acetate was refluxed seven hours. The cooled reaction mixture was washed with water and stirred with 300 ml saturated $NaHCO_3$ at 0°C for 45 minutes. The organic phase was dried over K_2CO_3 to yield a yellow oil which was distilled at atmospheric

pressure to give 35.41 g (31%) of 2-methyl-prop-1-enylacetate, b.p. 122-126°.
NMR ($CDCl_3$): δ 1.6 (s, 6H), 2.1 (s, 3H), 6.9 (mlt. 1H).

Step B: Preparation of 3,3-dimethyl-4-acetoxy-azetidin-2-one

Chlorosulfonyl isocyanate (16 ml) was added to a solution of 22.8 g (0.2 M) 2-methyl prop-1-enyl acetate in 50 ml methylene chloride at 0° under nitrogen. After stirring at 0° for 20 hours, the reaction mixture was added to a mixture of 20 ml water, 90 g ice, 48 g $NaHCO_3$ and 16.6 g Na_2SO_3 and stirred at 0° for 30 minutes. This was then extracted with 300 ml CH_2Cl_2 and the organic phase washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give 27.75 g oil which was chromatographed on silica gel in hexane/ethyl acetate to yield 2.17 g (8.5%) of 3,3-dimethyl-4-acetoxy-azetidin-2-one.
NMR ($CDCl_3$): δ 1.2 (s, 3H), 1.3 (s, 3H), 2.2 (s, 3H), 5.6 (s, 1H).

Step C: Preparation of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one

A mixture of 283.3 mg (1.8 mM) 3,3-dimethyl-4-acetoxyazetidin-2-one, 2 ml pyridine and 2 ml acetic anhydride was heated to 100° in a sealed tube for 36 hours. The reaction mixture was concentrated in vacuo and the residue chromatographed on silica gel in hexane/ethyl acetate to yield 295 mg (82%) of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one.
NMR ($CDCl_3$): δ 1.2 (s, 3H), 22 (s, 3H), 2.5 (s, 3H), 6.1 (s, 1H).

EXAMPLE 3

1-Acetyl-4-acetoxy-3-n-propylaztidin-2-one

Step A: Preparation of Pent-1-enyl acetate

A mixture of 86 g (1M) valeraldehyde, 153 g (1.5 M) acetic anhydride, and 12 g (0.125 M) potassium acetate, was refluxed for 8 hours. The cooled mixture was then stirred with 100 ml saturated aqueous $NaHCO_3$ for one hour. The organic phase is separated, dried over K_2CO_3, and distilled at 40 mm to yield 46.15 g (45%) of pent-1-enylacetate, b.p. 89°C.

NMR ($CDCl_3$): δ 1.0 (tr, 3H), 1.2-2.0 (mlt., 4H), 2.1 (s, 3H), 4.7-5.6 (mlt. 1H), 7.0-7.3 (mlt., 1H).

Step B: Preparation of 4-acetoxy-3-n-propylazetidin-2-one

Eight hundred microliters of chlorosulfonyl isocyanate was added to a solution of 1.28 g (10 mM) pent-1-enyl acetate in 5 ml methylene chloride at 0° under nitrogen. After stirring at 0° 5 days, the reaction mixture was added dropwise to a mixture of 5 g ice, 1.15 ml water, 2.82 g $NaHCO_3$ and 1.0 g Na_2SO_3 and stirred at 0° for 30 minutes. The mixture was extracted with 2 X 25 ml methylene choride and the combined organic phases washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 60 mg *trans* 4-acetoxy-3-n-propylazetidin-2-one (3.4%).

NMR ($CDCl_3$): δ 1.0 (mlt., 3H), 1.7 (mlt., 4H), 2.2 (s, 3H), 3.2 (tr, 1H), 5.6 (s, 1H), 6.7 (lrs, 1H).

Step C: Preparation of 1-acetyl-4-acetoxy-3-n-propyl-azetidin-2-one

A mixture of 56 mg (0.33 mM) 4-acetoxy-3-propylazetidin-2-one, 1 ml acetic anhydride and 1 ml pyridine was stirred at 100° in a sealed tube for 24 hours. After concentrating in vacuo the residue was chromatographed on silica gel in hexane/ethyl acetate, to yield 16 mg (23%) 1-acetyl-4-acetoxy-3-n-propyl-azetidine-2-one.

NMR ($CDCl_3$): δ 1.0 (br tr, 3H), 1.7 (mlt., 4H), 2.2 (s, 3H), 2.4 (s, 3H), 3.2 (tr, 1H), 6.1 (d, 1H).

EXAMPLE 4

1-Acetyl-4-methylsulfonylazetidin-2-one

Step A: Preparation of 1-acetyl-4-methylthioazetidin-2-one

A mixture of 300 mg (2.6 mM) 4-methylthio-azetidin-2-one, 10 ml acetic anhydride and 10 ml pyridine was stirred at 100° in a sealed tube 24 hours. After concentrating in vacuo, the residue was chromatographed on silica gel in hexane/ethyl acetate to yield 324 mg (78%) of 1-acetyl-4-methylthio-azetidine-2-one.

NMR ($CDCl_3$): δ 2.4 (s, 3H), 2.41 (s, 3H), 3.2 (doublet-quartet, 2H), 5.1 (doublet-doublet, 1H).

Step B: Preparation of N-acetyl-4-methylsulfinyl-azetidin-2-one

A mixture of 130 mg (0.82 mM) N-acetyl-4-methylthioazetidinone and 200 mg (0.93 nM) 80% m-chloroperbenzoic acid in 5 ml methylene chloride was stirred at room temperature 5 minutes. After

removing the solvent in vacuo. The residue was chromatographed on 2-2000 μ silica gel plates in hexane/ethyl acetate to yield 57 mg (40%) of 1-acetyl-4-methylsulfinylazetidine-2-one.
NMR ($CDCl_3$): δ 2.4 (s, 3H), 2.6 (s, 3H), 3.5 (mlt., 2H), 4.9 (mlt., 1H).

EXAMPLE 5

3-Azido-4-carboethoxy-1-(p-methoxyphenyl)-azetidin-2-one

To a solution of 3.06 g of azidoacetyl chloride in 50 ml of CH_2Cl_2 was added dropwise a solution of 3.57 ml of triethylamine and 5.3 g of the imine formed from ethylglyoxalate and p-anisidine in 50 ml CH_2Cl_2, with cooling at such a rate that the reaction temperature remained below 5°. The reaction was then stirred at room temperature for three hours and then washed sequentially with 1N HCl, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate, filtered, and evaporated, and the crude residue was recrystallized from carbon tetrachloride/hexane to afford 3.7 g. of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)azetidine-2-one; m.p. 80-85°.
NMR ($CDCl_3$): δ 7.2 (d, J=9, 2H), 6.75 (d, J=9, 2H), 4.9 (d, J=6, 1H), 4.6 (d, J=6; 1H), 4.25 (q, J=8, 2H), 3.7 (s, 3H), 1.25 (t, J=8, 3H).

EXAMPLE 6

4-Carboethoxy-3-chloro-1-(p-methoxyphenyl)-azetidine-2-one

4-carboethoxy-3-chloro-1-(p-methoxyphenyl)-azetidine-2-one was prepared by following the same procedure as described in Example 5 but using chloroacetyl chloride and the imine formed from ethylglyoxalate and p-anisidine as the starting material. The crude product was recrystallized from ether (hexane) to give 3.1 g of 4-carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one, m.p. 99-100°.

NMR ($CDCl_3$): δ 7.2 (d, J=9, 2H), 6.8 (d, J=9, 2H), 5.1 (d, J=6, 1H), 4.7 (d, J=6, 1H), 4.25 (q, J=7, 2H), 3.7 (s, 3H), 1.25 (t, J=7, 3H).

EXAMPLE 7

4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)-azetidine-2-one

4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)-azetidine-2-one was prepared by following the same procedure as described in Example 5 but using methoxyacetyl chloride as the starting material. After chromatography the compound crystallized as a white solid; m.p. 116-118°.

NMR ($CDCl_3$): δ 7.2 (d, J=9, 2H), 6.75 (d, J=9, 2H), 4.7 (d, J=5, 1H), 4.6 (d, J=5, 1H), 4.2 (q, J=5, 2H), 3.7 (s, 3H), 3.5 (s, 3H), 1.2 (t, J=5, 3H).

EXAMPLE 8

4-Carboethoxy-1-(p-methoxyphenyl)-3-phenyl-azetidin-2-one

To a solution of 17 ml of triethylamine and 5.0 g of the imine formed from ethyl glyoxalate and p-anisidine in 100 ml of refluxing 1,2-dichloroethane was added dropwise over 2 hours a solution of 16 ml of freshly distilled phenylacetyl chloride in 50 ml of dichloroethane. After refluxing for three hours the reaction was worked-up as per the 3-azido-azetidinone. The crude residue was chromatographed to yield the cis and trans isomers of 4-carboethoxy-1-(p-methoxyphenyl)-3-phenylazetidin-2-one as oils; cis: NMR ($CDCl_3$): δ 7.2 (m, 7H), 6.7 (d, J=9, 2H), 4.7 (s, 2H), 3.6 (s, 3H), 3.6 (q, J=7, 2H), 0.7 (t, J=7, 3H); trans: NMR ($CDCl_3$): δ 7.3 (m, 7H), 6.8 (d, J=9, 2H), 4.5 (d, J=2, 1H), 4.45 (d, J=2, 1H), 4.1 (q, J=7, 2H), 3.6 (s, 3H), 1.2 (t, J=7, 3H).

EXAMPLE 9

4-Carboethoxy-1-(p-methoxyphenyl)-3-vinylazetidin-2-one

4-Carboethoxy-1-(p-methoxyphenyl)-3-vinyl-azetidine-2-one was prepared by following the same procedure as described in Example 8 but using crotonyl chloride as the reagent. After chromatography the cis and trans isomers of the compound were obtained; cis (m.p. 70-72°), NMR ($CDCl_3$): δ 7.2 (d, J=9, 2H), 6.8 (d, J=9, 2H), 5.2-5.8 (m, 3H), 4.6 (d, J=6, 1H), 4.2 (m, 3H), 3.7 (s, 3H), 1.2 (t, J=7, 3H); trans (oil), NMR ($CDCl_3$): δ 7.25 (d, J=9, 2H), 6.8 (d, J=9, 2H), 5.7-6.2 (m, 1H), 5.2-5.5 (m, 2H), 4.25 (br.s., 1H), 4.2 (q, J=7,

2H), 3.9 (dd, J=1, Jz=6, 1H), 3.75 (s, 1H), 1.25 (t, J=7, 3H).

EXAMPLE 10

4-Carboethoxy-3-ethyl-1-(p-methoxyphenyl)azetidin-2-one

The cis and trans isomers of 4-carboethoxy-3-vinyl-1-(p-methoxyphenyl)azetidine-2-one are each hydrogenated with palladium on carbon in ethanol to yield the corresponding cis and trans isomers of 4-carboethoxy-3-ethyl-1-(p-methoxy-phenyl)azetidine-2-one.

EXAMPLE 11

4-Carboethoxy-1-(p-methoxyphenyl)-3-(N-methyl-trifluoroacetamido)azetidin-2-one

A solution of 2.16 g of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)-azetidine-2-one in ethanol was hydrogenated with palladium to yield 4-carboethoxy-1-(p-methoxyphenyl)-3-aminoazetidin-2-one. This amine was acylated with 1.1 ml of trifluoro acetic anhydride in 10 ml CH_2Cl_2 containing 1.5 ml pyridine, followed by methylation using 1 ml dimethyl sulfate in 30 ml acetone containing 3 g potassium carbonate. After isolation, the crude product was crystallized to give 2.2 g of 4-carboethoxy-1-(p-methoxyphenyl)-3-(N-methyl-trifluoroacetamido)-azetidine-2-one, m.p. 102-104°. NMR ($CDCl_3$): δ 7.2 (d, J=9, 2H), 6.75 (d, J=9, 2H), 5.5 (d, J=6, 1H), 4.7 (d, J=6, 1H), 4.2 (q, J=7, 2H), 3.7 (s, 3H), 3.2 (br.s., 3H), 1.2 (t, J=7, 3H).

EXAMPLE 12

4-Carboethoxy-3-methoxyazetidin-2-one

To a solution of 1.4 g of 4-carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one in 50 ml acetonitrile at 0° was added a solution of 8.23 g of cerric ammonium nitrate in 50 ml H_2O over 3 minutes. After stirring at 0° for 1 hour the solution was poured into 200 ml of 10% sodium sulfite and extracted with 3 X 75 ml of ethyl acetate. The combined organic extracts were washed with 10% sodium sulfite and saturated sodium chloride solutions and dried over sodium sulfate. Filtration and evaporation gave an amber oil which was recrystallized from methylene chloride/hexane to give 700 mg of 4-carboethoxy-3-methoxyazetidine-2-one; m.p. 91-92°.

NMR ($CDCl_3$): δ 7.1 (br.s, 1H), 4.7 (dd, J_1=2, J_2=5, 1H), 4.3 (d, J=5, 1H), 4.15 (q, J=7, 2H), 3.4 (s, 3H), 1.25 (t, J=7, 3H).

Following substantially the same procedure as described in Example 12 but using an appropriate 3-substituted azetidinone compounds (a) - (f) were prepared:

(a) 4-Carboethoxy-3-chloroazetidin-2-one

NMR ($CDCl_3$): δ 7.3 (br.s., 1H), 5.0 (dd, J_4=2, J_2=6, 1H), 4.4 (d, J=6, 1H), 4.2 (q, J=7, 2H), 1.3 (t, J=7, 3H).

(b) 4-Carboethoxy-3-phenylazetidin-2-one-2-(cis and trans)

NMR ($CDCl_3$): cis: δ 7.2 (s, 5H), 6.4 (br.s., 1H), 4.7 (d, J=6, 1H), 4.4 (d, J=6, 1H), 3.7 (q, J=7, 2H), 0.75 (t, J=7, 3H); trans: δ 7.2 (s,

5H), 6.9 (br.s, 1H), 4.3 (br.d, J=2, 1H), 4.1 (q, J=7, 2H), 4.0 (d, J=2, 1H), 1.2 (t, J=7, 3H).

(c) 4-Carboethoxy-3-(N-methyltrifluoroacetamido) azetidin-2-one

NMR ($CDCl_3$): δ 7.2 (br.s., 1H), 5.4 (d, J=6, 1H), 4.5 (d, J=6, 1H), 4.15 (q, J=7, 2H), 3.2 (s, 3H), 1.2 (t, J=7, 3H).

(d) 4-Carboethoxy-3-vinylazetidin-2-one(cis and trans)

NMR ($CDCl_3$) cis: δ 7.1 (br.s., 1H), 5.2-5.8 (m, 3H), 4.0-4.4 (m, 4H), 1.25 (t, J=7, 3H); trans: δ=7.25 (br.s., 1H), 5.0-6.2 (m, 3H), 4.1 (q, J=7, 2H), 3.9 (d, J=2, 1H), 3.7 (dd, J_1=2, J_2=7, 1H), 1.2 (t, J=7, 3H).

(e) 4-Carboethoxy-3-ethylazetidin-2-one

Cis: NMR($CDCl_3$): δ 6.9 (br. s., 1H); 4.2 (m, 3H); 3.4 (dd, J_1=6, J_2=8, 1H); 1.51 (q, J=8, 2H); 1.2 (t, J=7, 3H); 1.0 (t, J=8, 3H).

Trans: NMR($CDCl_3$): δ 6.8 (br. s., 1H); 4.2 (q, J=7, 2H); 3.8 (d, J=2, 1H); 3.2 (dd, J_1=2, J_2=7, 1H); 1.8 ((dq, J_1=2, J_2=8, 2H); 1.2 (t, J=7, 3H); 1.0 (t, J=8, 3H).

(f) 3-Azido-4-carboethoxyazetidin-2-one

EXAMPLE 13

4-Carboethoxy-3-(N-methyltrifluoroacetamido)-azetidine-2-one-1-sulfonic acid tetrabutylammonium salt

To a solution of 140 mg of 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one in 5 ml of pyridine at 80° was added 250 mg of sulfur trioxide pyridine complex, and the resulting mixture was stirred for 30 minutes at 80°. The solution was poured into 100 ml of 0.5 N KH_2PO_4 and extracted with 2 X 25 ml of methylene chloride. The combined organic washes were back-extracted with 25 ml of KH_2PO_4 solution. The combined aqueous phases were then treated with 680 mg of tetrabutylammonium hydrogen sulfate and extracted with 3 X 50 ml of methylene chloride. After drying (sodium sulfate) and evaporation of the organic phase the crude 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one-1-sulfonic acid tetrabutylammonium salt was chromatographed to yield an oil.

NMR ($CDCl_3$): δ 5.3 (d, J=6, 1H), 4.7 (d, J=6, 1H), 4.15 (q, J=7, 2H), 3.2 (m, 11H), 0.8-1.8 (m, 31H).

Applying the same procedure as described above, the following tetrabutylammonium salts of other azetidine derivatives were prepared:

(a) 4-Carboethoxy-3-methoxyazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

NMR ($CDCl_3$): δ 4.55 (d, J=6, 1H), 4.5 (d, J=6), 1H), 4.1 (q, J=7, 2H), 3.4 (s, 3H), 3.2 (m, 8H), 0.8-1.8 (m, 31H).

(b) 4-Carboethoxy-3-vinylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

EXAMPLE 14

4-Carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenyl-azetidin-2-one

To a solution of 720 mg of 4-carboethoxy-3-trans-phenylazetidin-2-one in 20 ml methylene chloride at 0° were added sequentially 595 mg of p-nitro-benzenesulfonyl chloride and 0.48 ml of DBU. The solution was stirred for several hours, diluted with 50 ml of methylene chloride, washed once with water and dried over sodium sulfate. Filtration and evaporation gave a crude residue which was chromatographed to yield pure 4-carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenyl-azetidin-2-one. NMR ($CDCl_3$): δ 8.3 (d, J=9, 2H), 8.2 (d, J=9, 2H), 7.2 (br.s., 5H), 4.0 (q, J=7, 2H), 3.7 (m, 2H), 1.2 (t, J=7, 3H). Similarly prepared was the corresponding cis-3-phenyl compound. NMR (CDCl3): δ 8.4 (d, J=9, 2H), 8.25 (d, J=9, 2H), 7.2 (s, 5H), 5.0 (s, 1H), 3.7 (m, 3H), 0.85 (t, 5=7, 3H).

Following the same procedure as described above but using appropriate reagents, the following compounds were prepared:

(a) 4-Carboethoxy-1-(p-nitrobenzensulfonyl)-3-vinyl-azetidin-2-one

NMR ($CDCl_3$): cis: δ 8.3 (d, J=9, 2H), 8.2 (d, J=9, 2H), 5.2-6.0 (m, 3H), 4.0-4.6 (m, 4H), 1.2 (t, J=7, 3H); trans: δ 8.2 (d, J=9, 2H), 8.15 (d, J=9, 2H), 5.2-6.0 (m, 3H), 3.9-4.4 (m, 4H), 1.25 (t, J=7, 3H).

(b) 4-Carboethoxy-3-ethyl-1-(p-nitrobenzenesulfonyl)-azetidin-2-one

(c) 3-Azido-4-carboethoxy-1-(p-nitrobenzenesulfonyl) azetidin-2-one

(d) 4-Carboethoxy-3-chloro-1-(p-nitrobenzensulfonyl)-azetidin-2-one

EXAMPLE 15

4-Carboethoxy-3-phenyl-1-trifluoromethanesulfenyl-azetidin-2-one

To a mixture of 1.2 g of 4-carboethoxy-3-phenylazetidin-2-one and 1.2 ml of triethylamine in 25 ml of methylene chloride at 0° was added dropwise over 10 minutes 11.25 ml of a 10% solution of trifluoromethanesulfenyl chloride in ether. After stirring for several hours the solution was washed with water, dried over sodium sulfate, filtered and evaporated. The crude residue was chromatographed to yield pure 4-carboethoxy-3-phenyl-1-trifluoro-methanesulfenylazetidin-2-one as an oil.
NMR ($CDCl_3$): δ 7.2 (s, 5H), 4.6 (d, J=3, 1H), 4.3 (m, 3H), 1.3 (t, J=7, 3H).

EXAMPLE 16

1-Tosyloxymethyl-3-n-Propyl-4-p-nitrophenylthio-azetidin-2-one

Step A: Preparation of 3-Propyl-4-p-nitrophenylthio azetidin-2-one

3-Propyl-4-acetoxy azetidinone, 171 mg. is refluxed with 200 mg p-nitrophenol thio in 10 ml benzene for 6 hours. The solution is washed 3x with aqueous Na_2CO_3, dried with $MgSO_4$, filtered and evaporated. The residue is chromatographed on silica

gel, eluting with 10:1 $CHCl_3$-EtOAc, affording 3-propyl-4-p-nitrophenylthioazetidin-2-one.

Step B: Preparation of 1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio azetidin-2-one

3-Propyl-4-p-nitrophenylthioazetidine-2-one, 266 mg, is stirred overnight at room temperature with 0.25 ml aqueous formalin (37%) and 17 mg K_2CO_3, Water and formaldehyde are removed in vacuo, and flushed with 2 ml pyridine. The residue is taken up in 4 ml pyridine and treated for 1 hour at room temperature with 200 mg p-toluenesulfonyl chloride. The pyridine is evaporated and replaced with 5 ml benzene. The solution is washed with aqueous H_3PO_4 and then aqueous K_2HPO_4, dried with $MgSO_4$, filtered and evaporated. The residue is chromatographed on silica gel, eluting with 25:1 $CHCl_3$-EtOAc, providing 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio-azetidin-2-one.

EXAMPLE 17

1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinyl-azetidin-2-one

1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenyl-sulfinylazetidin-2-one, 450 mg, is treated for 1/2 hour in 10 ml CH_2Cl_2 with 172 mg m-chloro-perbenzoic acid. The solution is washed with aqueous K_2HPO_4, dried with $MgSO_4$, filtered and evaporated, leaving pure 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinylazetidine-2-one.

EXAMPLE 18

1-Acetoxymethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one

Step A: Preparation of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one

3-n-Propyl-4-acetoxyazetidinone (1.164 g, 6.58 mmole) and 1.02 g (6.58 mmole) p-nitrothiophenol were heated in a tube in the steam bath for 3.5 hours. The reaction mixture was cooled, diluted with 100 ml ethyl acetate, and the organic phase was washed with 100 ml water, 70 ml 1M H_3PO_4 and 3x100 ml saturated K_2CO_3. The organic phase was dried over magnesium sulfate, filtered, and solvent removed *in vacuo* to yield 1.53 g of yellow crystals which were chromatographed on a silica gel column in chloroform-ethyl acetate (4:1) to give 359 mg (19%) of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one. NMR ($CDCl_3$): δ 0.92 (tr, 3H), 1.2-1.6 (br m, 4H), 3.10 (tr, 1H), 4.91 (d, 1H), 7.0 (br s, 1H), 7.50 (d, 2H), 8.20 (d, 2H).

Step B: Preparation of 1-Acetoxymethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one

A mixture of 273 mg (0.94 mmole) azetidinone from Step A, 26.3 mg paraformaldehyde and 178 mg (0.56 mmole) cesium carbonate was stirred in 20 ml dry tetrahydrofuran at ambient temperature 16.5 hours under nitrogen. A mixture of 430 µl pyridine and 2.56 ml acetic anhydride was added to the reaction mixture and the stirring continued 5 more hours. The solvents were removed *in vacuo* to give 604 mg crude product which was chromatographed on a silica gel

flash column in hexane-ethyl acetate 3/1. This gave 102 mg (30%) of 1-acetoxymethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one.
NMR ($CDCl_3$): δ 1.0 (tr, 3H), 1.2-1.85 (br m, 4H), 2.1 (s, 3H), 3.22 (tr, 1H), 4.95 (d, 1H), 5.18 (ABBA pattern, J_1=30H_3, J_2=5H_3, 2H), 7.65 (d, 2H), 8.22 (d, 2H).

Step C: Preparation of 1-Acetoxymethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one

To a solution of 46 mg (0.127 mmole) azetidinone from Step B in 4 ml CH_2Cl_2 and 4 ml saturated aqueous $NaHCO_3$ was added 27 mg (0.127 mM) 80% m-chloroperbenzoic acid and the reaction mixture stirred vigorously 15 minutes. The phases were separated and the organic phase was dried over $MgSO_4$, filtered and stripped to yield 57 mg crude product which was chromatographed on a 1000 μ silica gel prep TLC plate in chloroform-ethyl acetate 4:1 to yield 15 mg (31%) of 1-acetoxymethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one.
NMR ($CDCl_3$): δ 0.93 (tr, 3H), 1.2-1.8 (br m, 4H), 2.1 (s, 3H), 3.55 (tr, 1H), 4.66 (d, 1H), 5.04 (AB pattern, J_1=3.4H_z, J_2=6H_z, 2H), 8.2 (d, 2H), 8.52 (d, 2H).

EXAMPLE 19

4-Acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

A solution of 82 mg (0.463 mmole) 3-propyl-4-acetoxy azetidin-2-one in 5 ml pyridine was heated to 80°. 221 Mg (1.39 mmole) sulfur trioxide-pyridine complex was added and the reaction

mixture stirred at 80° one hour. It was then poured into 100 ml 0.5M KH_2PO_4 (aqueous) and washed with 2x25 ml CH_2Cl_2. The combined organic washes were backwashed with 25 ml 0.5M KH_2PO_4. 157 Mg (0.463 mmole) Bu_4NHSO_4 was added to the combined aqueous phases. This was extracted with 2x25 ml CH_2Cl_2 and the combined extracts were dried over $MgSO_4$, filtered, and stripped in vacuo to yield 12.4 mg of an oily residue which was chromatographed on a small silica gel column, eluted first with 75 ml hexane/ethyl acetate (3:1) to remove starting material, then with 100 ml ethyl acetate/methanol (4:1) to yield 13 mg (5.7%) 4-acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt.

NMR ($CDCl_3$): δ 1.0 (m, 16H), 1.75 (br m, 20H), 2.16 (s, 3H), 2.90 (br s, H), 3.1 (tr, 1H), 3.3 (tr, 8H), 4.08 (br tr, 1H), 6.18 (s, 1H).

EXAMPLE 20

(3R,4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)phenoxyazetidin-2-one

Step A: Preparation of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 27.5 ml of diisopropylamine in 150 ml of THF at -20°C was added 73.5 ml of 2.4N n-butyl lithium in hexane. After 15 minutes, the solution was cooled to -70°C and a solution of 20 gm of (4S)-1-t-butyldimethylsilylazetidin-2-one-4-carboxylic acid in 75 mL of THF was added. The solution was warmed to -20°C for 15 minutes before a

solution of 13.5 mL of methyl iodide in 20 mL of THF was added. After 30 minutes at -20 to 0°C, the reaction was diluted with 300 mL of ether and then poured into a mixture of ice and 400 mL of 1N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from hexane to give 12-15 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid.
NMR ($CDCl_3$): δ .14 (2, 3H), .32 (s, 3H), .91 (d, 3H), .98 (s, 9H), 3.34 (dq, 1H), 3.71 (d, 1H)

Step B: Preparation of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 13 mL of diisopropylamine in 75 mL of THF at -20°C was added 35 mL of 2.4 M n-butyl lithium in hexane. After 15 minutes the solution was cooled to -70°C and a solution of 10 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid in 50 mL of THF was added. The solution was warmed to -20°C for 15 minutes and a solution of 6.7 mL of ethyl iodide in 10 mL of THF was added. After 30 minutes at -20° to 0°C the reaction was diluted with ether and poured into a mixture of ice and 1 N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were each washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from a minimum amount of hexane to give 8.8 gms of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid.

NMR($CDCl_3$): δ .15 (s, 3H), .31 (s, 3H), .98 (s, 9H), 1.04 (t, 3H), 1.22 (s, 3H), 1.78 (q, 2H), 3.94 (s, 1H).

Step C: Preparation of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one.

To a solution of 13.0 gms of (3R, 4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid in 75 mL of DMF and 15 mL of acetic acid under N_2 was added 23 gms of lead tetraacetate. The reaction was heated at 45-50°C for 18 hours and then poured into ice water and extracted into 2 portions of ether. The ether layers were washed with water, dilute sodium bicarbonate solution and brine, dried over sodium sulfate and evaporated to give 13 gm of crude oil containing a mixture of (3R, 4S) and (3R, 4R)-4-acetoxy-3-ethyl-3-methyl-azetidin-2-one. To this mixture in 50 mL of acetone was slowly added a solution of 14 gms of t-butyl 4-hydroxybenzoate in 50 mL of acetone, 5 mL of water and 29 mL of 2N sodium hydroxide. The reaction was stirred at room temperature for 64 hours and then diluted with water and extracted with 2 portions of ether. The ether layers were washed with brine, dried over sodium sulfate and evaporated. The residue was prep LC'ed with 15-25% ethylacetate/hexanes to give 6.3 gm of the higher R_f (4R) ether and 1.5 gm of the desired (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxy-azetidin-2-one.

NMR ($CDCl_3$): δ 1.0 (t, 3H), 1.38 (s, 3H), 1.54 (s, 9H), 1.6-2.0 (m, 2H), 5.30 (s, 1H) 6.7 (brs, 1H), 6.78 (d, 2H), 7.90 (d, 2H).

Step D: Preparation of (3R, 4S)-1-(benzylamino-carbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one

To a solution of 1.5 gm of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one in 25 mL of methylene chloride was added 1.2 mL of benzylisocyanate, 1.4 mL of triethylamine and 10 mg of 4-dimethylaminopyridine. The reaction was stirred at room temperature for 16 hours and then evaporated. The residue was flash chromatographed eluting with 10 to 25% EtoAc/Hexane to give 2.3 gm of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxy azetidin-2-one.
NMR ($CDCl_3$): δ .98 (t, 3H), 1.36 (s, 3H) 1.50 (s, 9H), 1.62 (m, 1H), 1.84 (m, 1H), 4.42 (d, 2H), 5.64 (s, 1H), 6.80 (brt, 1H), 7.06 (d, 2H), 7.24 (brs, 5H), 7.90 (d, 2H).

Step E: Preparation of (3R, 4S)-1-(benzylamino-carbonyl)-3-ethyl-3-methyl-4-(4-carboxy)-phenoxyazetidin-2-one

To 2.3 gm of (3R, 4S)-1-(benzylamino-carbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy) phenoxyazetidin-2-one in an ice bath under N_2 was added 5 mL of anisole and then 25 mL of precooled trifluoroacetic acid. After 1.5 hours at 0°C, the volatiles were removed in vacuo without heating and the residue flash chromatographed using hexane, then 15% EtoAc/Hexane, then 1% HoAc in 15% EtoAc/hexanes to give after ether trituration 1.8 gm of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)phenoxyazetidin-2-one.
NMR ($CDCl_3$): δ 1.03 (t, 3H), 1.46 (s, 3H), 1.66 (m,

1H), 1.94 (m, 1H), 4.50 (d, 2H), 5.76 (s, 1H), 6.9 (brt, 1H), 7.05 (d, 2H), 7.25 (brs, 5H), 7.98 (d, 2H).

EXAMPLE 21

t-Butyl 4-hydroxy-phenylacetate

A solution of H_2SO_4 (5 ml) in dioxane (80 ml) was added to 4-hydroxyphenylacetic acid (20 gm, 0.13 mol) in a pressure bottle. Isobutylene (250 ml) was added and the bottle was sealed and the mixture was stirred for 24 hr. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were washed successively with saturated $NaHCO_3$, H_2O (twice) and brine before being dried over Na_2SO_4 and evaporated to dryness. Crystals formed after standing overnight and they were filtered, washed with cold hexane and dried to give 20.99 gm of the title compound. M.pt. 95-96°C.
NMR: δ 1.45 (s, 9H), 3.45 (s, 2H), 4.60 (brs, 1H), 6.72 (d, 2H), 7.10 (d, 2H).

EXAMPLE 22

(R,S)-3,3-Diethyl-4-[(4-t-butoxycarbonylmethyl)-phenoxy]azetidin-2-one

Step A: Preparation of 1-acetyloxy-2-ethyl-1-butene

A solution of 2-ethylbutyraldehyde (600 gm, 5.99 mol), acetic anhydride (900 ml, 8.15 mol) and sodium acetate (61.5 gm) was heated to reflux under N_2 atmosphere. After 2 days the reaction was poured into a mixture of CH_2Cl_2 (1 liter), H_2O (1 liter) and ice (500 gm). The solution was neutralized by adding solid Na_2CO_3 and the layers were separated. The

aqueous layer was further extracted with CH_2Cl_2 and the pooled organic layers were washed with saturated NaCl, dried over Na_2SO_4 and evaporated to dryness. Distillation of the residue in vacuo gave 464.5 gm of the title compound.

Step B: Preparation of 4-acetyloxy-3,3-diethyl-azetidin-2-one

A solution of the material prepared in Step A (169 gm, 1.19 mol) in CH_2Cl_2 (300 ml) was cooled in an ice-ethanol bath under N_2 and chlorosulfonyl isocyanate (200 gm, 1.41 mol) was added via an addition funnel. The solution was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with Et_2O and added to ice-cold $NaHCO_3$ solution containing Na_2SO_3, keeping the solution below 5°C during the addition. After the evolution of gas had ceased, the layers were separated and the aqueous layer was extracted with Et_2O. The combined ether extracts were washed with H_2O, brine and then dried over Na_2SO_4 before being evaporated to dryness. This gave a dark oil which was diluted with hexane (100 ml) and cooled in the freezer for 2 days. The low melting white solid which formed was filtered off and washed with cold hexane to give 79.2 gm of the title compound.
NMR: δ 0.99 (t, 3H), 1.02 (t, 3H), 1.72 (m, 4H), 2.13 (s, 3H), 5.58 (s, 1H), 6.40 (brs, 1H).

Step C: Preparation of (R,S)-3,3-diethyl-4-[(4-t-butoxycarbonylmethyl)-phenoxy]azetidin-2-one

Material prepared in Example 21 (20.8 gm, 0.1 mol) was dissolved in 2N NaOH (100 ml) by

stirring for 15 min. and a solution of the material prepared in Step B above (18.5 gm, 0.1 mol) in toluene (100 ml) and hexane (100 ml) was added. The reaction mixture was vigorously stirred for 1 hr and then the layers were separated and the aqueous layer was extracted with EtOAc. The organic layer was washed with water, brine and dried over Na_2SO_4 before being evaporated to dryness. The residue so obtained was purified by preparative LC using 20% EtOAc-hexane to give 17.5 gm of the title compound.
NMR: δ 1.00 (t, 3H), 1.05 (t, 3H), 1.43 (s, 9H), 1.71-2.00 (m, 4H), 3.46 (s, 2H), 5.32 (s, 1H), 6.74 (brs, 1H), 6.82 (d, 2H), 7.20 (d, 2H).

EXAMPLE 23

Benzyl 4-hydroxy-phenyl acetate

To a solution of 4-hydroxyphenylacetic acid (3.969 Kg, 26.09 mol) in DMF (15.9 L) was added lithium carbonate (2.12 Kg, 28.7 mol) and the resulting mixture was stirred at room temperature for 10 minutes. Benzyl bromide (3.723 L, 31.3 mol) was added and the mixture was heated to 100°C (internal temperature) for 3 hours. The reaction was cooled to 60°C, 2N HCl (20 L) was added and the solution was extracted with EtOAc (2 x 10 L). The combined organic extracts were washed successively with saturated $NaHCO_3$ (16 L) and H_2O (3 x 16 L). Any emulsions formed during these extractions were broken up by the addition of toluene (20 L total). The EtOAc was removed by distillation until the level of EtOAc was <0.3% (additional toluene (5 L) was added during distillation). The volume of the mixture was reduced to 16 L and allowed to cool to room

temperature when crystallization occurred. The slurry was diluted with hexane (20 L) and aged at ambient temperature overnight, before being cooled to 0°C. The solid was filtered, washed with a cold mixture of toluene/hexane (1:1, 4 L) and dried in vacuo to give 5.283 Kg of the required product.

EXAMPLE 24

(R,S)-3,3-Diethyl-4-[(4-benzyloxycarbonylmethyl)-phenoxy]azetidin-2-one

Method A:

Step A: Preparation of 1-propionyloxy-2-ethyl-1-butene

A reaction vessel was charged sequentially with Et_3N (12.8 L), propionic anhydride (14.48 L), dimethylaminopyridine (94 gm) and 2-ethylbutyraldehyde (7.5 L). The mixture was stirred and heated under gentle reflux (120-135°C) for 5 hours in a nitrogen atmosphere. The reaction was then cooled to 70°C and H_2O (13.5 L) was added slowly. On complete addition, the mixture was heated at reflux for 45 minutes and then cooled to room temperature before hexane (7.5 L) was added. The aqueous layer was separated and re-extracted with hexane (5 L) and the combined organic layers were washed with saturated $NaHCO_3$ (2 x 7.5 L) before being evaporated in vacuo at 40°C. The residue (10 Kg) so obtained was fractionally distilled (b.p. 75-80°C, 30-40 mm Hg) to give the required product (7.712 Kg) as a mobile liquid.

Step B: Preparation of 4-propionyloxy-3,3-diethyl-azetidin-2-one

The product (2.5 Kg) prepared as described above in Example 24, Method A, Step A, was dissolved in nitromethane (1.25 L) and the solution was allowed to cool to -2°C overnight. Chlorosulfonyl isocyanate (2.1 L) was added over 30 minutes, maintaining the temperature below 6°C. On complete addition, the yellow solution was cooled to 0°C and stored under a nitrogen atmosphere for 30 hours. The reaction mixture was then diluted with Et_2O (4 L) and then added slowly over 30 minutes to a mixture of H_2O (70 L), Na_2SO_3 (7.5 Kg) and $NaHCO_3$ (12.5 Kg) at 5°C, maintaining the temperature below 5°C throughout the addition. An additional 2.5 L of Et_2O was used for washing-in. The reaction wa then allowed to rise to 15°C over 1 hour, after which time gas evolution had ceased. The reaction mixture was then filtered and rinsing was carried out with H_2O (10 L) and t-butylmethylether (15 L). The lower layer was separated and and further extracted with t-butylmethylether (15 L). The combined organic extracts were washed with brine (20 L), dried over Na_2SO_4, filtered and evaporated to dryness (temperature below 35°C to give the product (2.64 Kg) as a yellow oil suitable for use in the next step.

Step C: Preparation of (R,S)-3,3-diethyl-4-[(4-(benzyloxycarbonylmethyl)phenoxy]azetidin-2-one

A solution of benzyl 4-hydroxy-phenyl acetate (2.68 Kg, 11.07 mol, prepared as described above in Example 23) in toluene (65 L) was heated at

40°C until a solution was obtained and $Ba(OH)_2.8H_2O$ (4.20 Kg, 13.31 mol) was then added. This slurry was stirred at 40°C for 10 minutes and then a solution of 4-propionyloxy-3,3-diethylazetidin-2-one (2.57 Kg, 11.73 mol, prepared as described above in Example 24, Step B) in toluene (10 L) was added over 15 minutes. After 1.5 hours a second portion 4-propionyloxy-3,3-diethylazetidin-2-one (70 gm) was added. After an additional 30 minutes the mixture was cooled to 15°C and 2N HCl (30 L) was added. The organic layer was washed successively with saturated $NaHCO_3$ (2 x 30 L) and brine (20 L), and then was concentrated in vacuo to give 3.805 Kg of the product as a viscous yellow oil.)

Method B:

Step A: Preparation of 1-(2-ethylpropionyloxy)-2-ethyl-butene

2-Ethylbutyric anhydride (4.34L), 2-ethyl-butyraldehyde (2.28L), triethylamine (2.62L), and 4-dimethylaminopyridine (210g) were mixed and stirred under a N_2 blanket and the temperature was successively raised to 120°C over 1.5 hr, then 140°C over 8 hr, followed by maintenance at 140°C for 10 hr. The mixture was then cooled to 90°C, H_2O (2L) was added and the mixture was then heated at reflux for 1 hr before being allowed to cool to 25°C. To this material was then added H_2O (2L) and hexanes:EtOAc (3:1; 3L) and, after mixing, the layers were separated and the organic layer was washed successively with cold 2N HCl (3L) and sat. $NaHCO_3$ (3 x 2L) before being concentrated in vacuo and then

flushed with EtOAc (500mL). This afforded 3.7kg of crude product which was purified by distillation (b.p. 80°C/1mm Hg) to give 3.3kg of the title compound as a clear colorless oil.

Step B: Preparation of 3,3-diethyl-4-(2-ethylpropionyloxy)-azetidin-2-one

The material prepared above in Example 24, Method B, Step A (3.3kg) was cooled to 5°C under a N_2 blanket and chlorosulfonyl isocyanate (2.1L) was added with stirring over 1 hr. The mixture was then stirred at 8°C for 45 hr and then cooled to 0°C, diluted with toluene (5L), and then added to a mixture of H_2O (60L), ice (20L), $NaHCO_3$ (13kg) and Na_2SO_3 (7.5kg). This mixture was stirred at 20°C for 13 hr before being filtered through Celite. The pad was washed with EtOAc (7L) and the two layers of the filtrate were separated. The aqueous layer was further extracted with EtOAc (12L) and the combined organic layers were washed with brine (8L) before being concentrated in vacuo. Toluene (2L) was then added to the residue and the solution was re-concentrated to dryness to give 4.57kg of a light yellow oil which was of sufficient purity for use in the next step.

Step C: Preparation of (R,S)-3,3-diethyl-4-[(4-benzyloxycarbonylmethyl)phenoxy]-azetidin-2-one

Benzyl 4-hydroxyphenylacetate (2.6kg) was dissolved in DMF (20L) and H_2O (2.8L) and milled K_2CO_3 (4.5kg) were added. To this mixture (at 35°C) was added the material prepared above in Example 24, Method B, Step B (3.15kg of β-lactam). The resulting

mixture was cooled and stirred at 30 - 31°C for 1 hr, followed by stirring at 18°C for an additional hr before being quenched by the addition of 2N HCl (15L) and EtOAc (15L). The layers were separated and the aqueous phase (pH 8.2) was further extracted with EtOAc (18L). The combined organic layers were washed successively with sat. $NaHCO_3$ (13L), H_2O (10L), and brine (10L) before being concentrated in vacuo to afford the title compound as a yellow-orange oil (5.4kg) which was of sufficient purity for use in the next step.

Method C:

A solution of the material prepared in Example 24, Method A, Step B (2.2 gm, 11.9 mmol), benzyl 4-hydroxyphenylacetate (2.93 gm, 12.1 mmol), cinchonin (0.35 gm, 1.2 mmol) and powdered anhydrous Na_2CO_3 (1.28 gm, 12.1 mmol) in toluene (25 ml) was heated to 60°C for 72 hr. After cooling, EtOAc (100 ml) was added and the solution was washed successively with 1N HCl (3 x 25 ml), sat. $NaHCO_3$ solution (25 ml), H_2O (25 ml), and brine (25 ml). The solution was then dried over Na_2SO_4, filtered and evaporated to dryness to give a clear, yellow oil which was purified by flash chromatography (silica gel, 25% EtOAc in hexanes) to give the title compound as a slightly yellow oil (3.05 gm). $[\alpha]_D$ -23.70 NMR (CDCl3): δ 1.08 (t, 3H), 1.12 (t, 3H), 1.64 - 2.14 (m, 4H), 3.48 (s, 2H), 5.18 (s, 2H), 5.38 (s, 1H), 6.90 (d, 2H), 7.28 (d, 2H), 7.40 (s, 5H).

EXAMPLE 25

(R,S)-3,3-Diethyl-4-[(4-carboxymethyl)phenoxy]-azetidin-2-one

(R,S)-3,3-Diethyl-4-[(4-benzyloxycarbonyl-methyl)phenoxy]azetidin-2-one (5.24 Kg, (14.26 mol) prepared as described above in Example 24, Method A was dissolved in alcohol (34.5 L) and cyclohexene (10.5 L) containing 10% PdC (524 gm). The mixture was stirred and heated under reflux for 3 hours and then allowed to cool to room temperature before being filtered through Whatman GFA paper to remove the catalyst. The pad was washed with EtOAc and the combined filtrates were evaporated to dryness to give a viscous oil. This was partitioned between 10% aq. K_2CO_3 (6 L) and EtOAc (7 L) and the lower layer was re-extracted with EtOAc (7 L). The aqueous layer was acidified with 5N HCl (N4.8L) and extracted with EtOAc (10L). The lower aqueous layer was separated and re-extracted with EtOAc (7L). The pooled organic layers were washed with H_2O (5 L), dried over Na_2SO_4, filtered and evaporated in vacuo to give a viscous oil which solidified upon storage in the cold room giving 3.55 Kg of the required product.

EXAMPLE 26

(S)-3,3-Diethyl-4-[(4-carboxymethyl)phenoxy]azetidin-2-one,(S)-(-)-α-methylbenzylamine salt

The racemate (253.3 gm, 0.91 mol) prepared as described above in Example 25 was dissolved in EtOAc (1.27 L) and (R)-(+)-α-methylbenzylamine (117.7 mL, 0.91 mol) was added followed by a seed crystal of

(R)-3,3-diethyl-4-[(4-(carboxymethyl)phenoxy]azetidin-2-one, (R)-(+)-α-methylbenzylamine salt. This mixture was stirred at room temperature overnight and then chilled to 0-5°C for 1 hour, filtered, washed with a little cold EtOAc and dried in air. This material was swished in EtOAc (1.2 L) at 60°C for 1 hour and then cooled to 0-5°C for 1.5 hour, filtered and washed with a little fresh solvent. All of the filtrates and the swish were combined and washed successively with 2N HCl (3 x 350 mL) and brine (1 x 350 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to give a viscous oil (187 gm). This oil was dissolved in EtOAc (935 mL) and treated with (S)-(-)-α-methylbenzylamine as described above for the crystallization of the unwanted isomer with (R)-(+)-α-methylbenzylamine. This gave 119.84 gm of the desired (S)-3,3-diethyl-4-[(4-carboxy-methyl)-phenoxy]azetidin-2-one, (S)-(-)-α-methyl-benzylamine salt with an enantiomeric purity 98%. Reworking of the mother liquors gave an additional 18.8 gm (i.e. total yield of 138.64 gm).

EXAMPLE 27

(S)-3,3-Diethyl-4-[(4-benzyloxycarbonylmethyl)-phenoxy]azetidin-2-one

The resolved material prepared as described above in Example 26, (3.35 Kg, 8.41 mol) was partitioned between EtOAc (21 L) and 2N HCl (4.2 L), with stirring for 15 min. The organic layer was washed successively with 2N HCl (2 x 4.2 L) and H_2O (2 x 5 L) and then dried over Na_2SO_4, filtered and evaporated to dryness to give 2.36 Kg of the resolved acid. This oil was dissolved in DMF (11.8 L) and

stirred overnight with ground K_2CO_3 (698 gm, 5.05 mol) and benzyl bromide (1.02 L, 8.57 mol) at room temerature. Water (26 L) was then added and the mixture was extracted with t-butylmethyl ether (14 L). The lower layer was re-extracted with t-butylmethyl ether (14 L) and the combined organic layers were washed with H_2O (2 x 10 L), dried (Na_2SO_4), filtered and evaporated to dryness to give the product (2.87 Kg) as a viscous oil. $[\alpha]_D$ = -60.8° (c = 1.0, 1,1,1-trichloroethane).)

EXAMPLE 28

(R)-α-Allyl-4-methylbenzyl isocyanate

Method A:

Step A: Preparation of (R)-α-allyl-4-methyl-phenyl-benzylamine, L-pyroglutamic acid salt

A solution of lithium bistrimethylsilylamide was prepared as follows. To hexamethyldisilazane (4.04 Kg, 5.28 L, 25 mol) was added anhydrous THF (4 L). The solution was cooled to -5°C and n-BuLi (2.4 M in hexanes, 9.7 L) was added over a period of 1.5 hr, while maintaining the reaction temperature between -5 and 0°C. The mixture was then aged for 10-15 min, allowed to rise to room temperature and stored under N_2 overnight.

A solution of p-tolualdehyde (2.91 Kg, 24.27 mol) in THF (10 L) was cooled under N_2 to -8°C and the solution of lithium bistrimethylsilylamide prepared above was added via an addition funnel, while maintaining the reaction temperature between -8 and 0°C. The mixture was then warmed to 10°C and

allylmagnesium chloride (2 M, 12.5 L, 25 mol) was added, while maintaining the temperature between 15 - 20°C. After aging for 15 min the reaction mixture was cooled to 10°C and transferred to a larger vessel containing H_2O (85 L) and NH_4Cl (12 Kg) at 10°C. An additional 5 L of THF was used to complete the transfer and the quench mixture exothermed to 25°C during the transfer. After stirring for 30 min the lower aqueous layer separated and was removed. The organic layer was washed with brine (20 L) and then the bulk solvent was removed in vacuo at 30 - 35°C and the remaining solution (8 - 10 L) was dried over Na_2SO_4, filtered and evaporated to dryness to give the product racemic amine in quantitative yield.

This racemate (3.95 Kg, 23.8 mol) was dissolved in EtOAc (40 L) and this solution was added to a solution (warming to 50°C was necessary to effect complete dissolution) of L-pyroglutamic acid (1.84 Kg, 14.26 mol) in methanol (8 L). The mixture was heated to reflux and solvent (20 L) was distilled from the vessel. EtOAc (30 L) was added and more solvent (30 L) was distilled off. A further charge of EtOAc (40 L) was added and the reaction mixture was concentrated to 39 L. The mixture was allowed to cool to 65°C and seeded before being allowed to cool further (to 50°C over 30 min) to form a thick slurry. The slurry was then reheated to reflux and aged for 30 min. After cooling to room temperature over 1 hr, and further aging at 15°C for 1 hr, the amine salt was filtered, washed with EtOAc (3 L) and dried in vacuo at 50°C. This material was recrystallized from EtOAc (23 L), filtered, washed succesively with EtOAc (2 x 2 L) and Et_2O (1 L) and

then dried in vacuo overnight at 50°C to give the title amine salt with an R:S ratio (GC of menthyl carbamate derivatives) of 95:5.

Step B: (R)-α-Allyl-4-methylbenzyl isocyanate

The amine salt prepared above in Example 28, Method A, Step A (2.655 Kg) was dissolved in a mixture of t-butylmethyl ether (7.38 L) and H_2O (7.38 L) and 5M NaOH (3 L) was added. This mixture was stirred for 15 min and the aqueous layer was separated and re-extracted with t-butylmethyl ether (7.38 L). The pooled orgnaic extracts were washed with brine (2 x 4 L), dried (Na_2SO_4), filtered and evaporated to dryness to give the free amine (1.5 Kg) as a mobile liquid. This material was dissolved in EtOAc (8.86 L) and cooled to 0 - 5°C and to this was added a solution of EtOAc/HCl (prepared separately by adding absolute EtOH (1.062 L) dropwise over 50 min to an ice cold solution of acetyl chloride (1.298 L) in EtOAc (3.54 L), while maintaining the temperature below 10°C during the addition) dropwise over 50 min, maintaining the temperature below 20°C. The resulting amine hydrochloride slurry was heated to 70°C and a solution of 1.93M phosgene in toluene (11 L, 21.1 mol) was added over 1.75 hr at this temperature. The resulting solution was heated at 70°C for a further 1.75 hr and then cooled to room temperature. A mixture of brine (6 L) and H_2O (6 L) was added and the mixture allowed to separate. The organic phase was washed successively with saturated $NaHCO_3$ solution (2 x 10 L) and brine (10 L) before being dried over Na_2SO_4, filtered and evaporated to dryness to give the title compound as a mobile liquid.

Method B:

Step A: Preparation of (R)-α-allyl-4-methyl-benzylamine

A solution of lithium bistrimethylsilylamide was prepared by adding 208 ml of 2.5M n-BuLi to a solution of bistrimethylsilylamine (110 ml, 0.52 mol) in THF (140 ml) at 0°C. After stirring for 15 min, this solution was added via a cannula to a solution of p-tolualdehyde (59 ml, 0.5 mol) in THF (100 ml), while keeping the temperature between -40 and -50°C. The reaction mixture was then allowed to warm up to 10°C over 30 min. A 2M solution of allyl magnesium chloride (260 ml) in THF was added, keeping the temperature of the reaction between 10 and 15°C. After stirring for 30 min the reaction was poured into a solution prepared by dissolving NH_4Cl (150 gm) in H_2O (1 liter). The layers were separated and the aqueous layer was extracted with Et_2O - hexane. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The residual oil was added to a solution of (1R)-(-)-10-camphorsulfonic acid (62.5 gm) in EtOAc (1 liter) with cooling. On standing overnight at room temperature, crystals were formed and these were filtered off and washed with EtOAc. The solid was stirred with refluxing EtOAc (300 ml), filtered and washed again with EtOAc. The pure product so formed weighed 60.7 gm (59%). $[\alpha]_D$ -27.16 (c = 0.5, EtOH).

Step B: (R)-α-allyl-(4-methylphenyl)methyl isocyanate

A slurry of 50 gm (0.122 mol) of material prepared as described above in Step A was added to 2N NaOH (75 ml) and Et_2O (150 ml). After stirring for 5 min the layers were separated and the aqueous layer was extracted with Et_2O. The pooled organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness.

A 3-necked flask equipped with a gas inlet tube, a condenser, and an addition funnel without sidearm was charged with EtOAc (100 ml) and this was heated on a 60°C bath while phosgene gas was bubbled through the solution. A solution of the amine obtained above in 20 ml of EtOAc was added dropwise at a rate such that the white solid did not build up in the reaction mixture. Phosgene was continued for 5 additional minutes after all the amine had been added and the solution was clear. The bath was then heated to 110°C and EtOAc was removed by distillation. The title compound was so obtained as a yellow residue (24.99 gm) and was used without further purification.

EXAMPLE 29

(4S)-3,3-Diethyl-1-[(R)-α-n-propyl-(4-methyl)benzyl-aminocarbonyl]-4-[4-(carboxymethyl)phenoxy]azetidin-2-one

Step A: Preparation of (4S)-3,3-Diethyl-1-[(R)-α-allyl-(4-methyl)benzylaminocarbonyl]-4-[4-(benzyloxycarbonylmethyl)phenoxy]azetidin-2-one

To a vessel charged with DMF (14.23 L) was

added the material prepared above in Example 27 (2.845 Kg, 7.74 mol) and the material prepared above in Example 28, Method A (8.17 mol). Ground, anhydrous K_2CO_3 (108 gm, 0.78 mol) was added and the resulting mixture was stirred at room temperature, under N_2, for 2.5 hr. The reaction mixture was then diluted with EtOAc (25 L) and stirred with H_2O (25 L) for 5 min. The layers were separated and the organic layer was washed with H_2O (25 L). An emulsion formed which was broken up by the addition of saturated brine (5 L) and the organic layer was further washed with H_2O (2 x 20 L). Again emulsions were formed and this time they were broken up by the addition of t-butylmethyl ether (10 L). The organic layer was finally washed with brine (10 L) and then concentrated in vacuo to 12 L, dried over Na_2SO_4, filtered and evaporated to dryness to give the title compound as a viscous orange oil which was suitable for use in the next step.

Step B: (4S)-3,3-Diethyl-1-[(R)-α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[4-(carboxy-methyl)phenoxy]azetidin-2-one, iso-butanolamine salt

The material prepared above in Example 29, Step A (1.547 Kg), was dissolved in a mixture of t-butanol (7.347 Kg) and H_2O (387 mL) containing 10% Pd/C (150 gm) and hydrogenated at 50 psi for 1 hr at 20°C. The mixture was then filtered through Hyflo and the pad was washed with EtOAc. The filtrate was evaporated to dryness to give the title compound (free acid) as a viscous oil in essentially quantitative yield. Two more runs gave a total of

4.2 Kg of crude free acid (estimated 3.5 Kg of desired material by LC and NMR analysis) which was dissolved in t-butylmethyl ether (50 L) at room temperature. A solution of 2-amino-2-methyl-1-propanol (670 gm) in t-butylmethyl ether (13 L) was added over 20 min at room temperature. The solution was seeded and the resulting slurry was stirred at room temperature overnight. The mixture was then chilled at 0°C for 1 hr, filtered, washed with t-butylmethyl ether (12 L) and dried in vacuo at room temperature. This product was recrystallized twice from EtOAc to give the title compound (3.159 Kg) as a crystalline white powder. m.p. 138.5 - 140°C.

EXAMPLE 30

(S)-3,3-Diethyl-4-[(4-allyloxycarbonylmethyl)-phenoxy]azetidin-2-one

Method A:

The resolved material prepared above in Example 26, (19.9 gm, 0.05 mol) was added to a mixture of ice-H_2O (300 mL), conc. HCl (5 mL), and Et_2O and mixed thoroughly until dissolution occured. The layers were separated and the aqueous layer was extracted with Et_2O. The pooled Et_2O layers were washed successively with H_2O and sat. NaCl before being dried over Na_2SO_4, filtered and evaporated to dryness. This residual oil was dissolved in DMF (100 mL) and powdered K_2CO_3 (7.1 gm, 0.051 mol) was added, followed by allyl bromide (4.6 mL, 0.053 mol). This mixture was stirred overnight at room temperature and was then partitioned between H_2O and Et_2O. The

layers were separated and the aqueous layer was extracted with Et_2O. The pooled Et_2O layers were washed with H_2O (2x) and sat. NaCl before being dried over Na_2SO_4, filtered and evaporated to dryness to give 17.0 gm (0.05 mol, quantitative yield) of the title compound suitable for use in the next step. NMR ($CDCl_3$, δ from TMS): 1.03 (t, 3H, J = 7Hz), 1.06 (t, 3H, J = 7Hz), 1.65 - 2.05 (m, 4H), 3.60 (s, 2H), 4.59 (d of t, 2H, J = 6Hz, J = 1Hz), 5.2 - 5.4 (m, 2H), 5.34 (s, 1H), 6.57 (br s, 1H), 6.82 (m, 2H), 7.27 (m, 2H)

EXAMPLE 31

(R)-5-[(1-Isocyanate)butan-1-yl]benzofuran

Step A: Preparation of (4-Bromo-2-formyl)phenoxy-acetic acid, monohydrate

To a solution of 5-bromosalicylaldehyde (5kg) in THF (12.1L) at 40°C under a N_2 blanket was added a solution of bromoacetic acid (3.8kg) in H_2O (50L). This mixture was stirred at 40°C and a solution of NaOH (2.09kg) in H_2O (8.1L) was added over 20 min. The deep red solution so formed was warmed to gentle reflux for 18 hr. THF (approx. 7L) was then distilled from the reaction mixture at atmospheric pressure and the resultant yellow solution was cooled to room temperature. The pH was then adjusted to 8 ± 0.2 by the addition of sat. $NaHCO_3$ solution and the resultant mixture was extracted with isopropylacetate (2 x 15L). The aqueous layer was acidified to pH 3 ± 0.2 with conc. HCl (2.4L) and the resultant slurry was aged at 20°C

for 1 hr and the product was then filtered off, washing the pad with H_2O (7L) to give the title compound as a pale yellow solid (3.77kg).

Step B: Preparation of 5-bromobenzofuran

A slurry of the material prepared above in Example 31, Step A (3.70kg) and sodium acetate (7.40kg) in acetic acid (18.5L) was heated to gentle reflux under a N_2 blanket and acetic anhydride (7.4L) was then added dropwise over 6 hr. This mixture was then heated at reflux until HPLC indicated no remaining starting material. The reaction was then cooled to 80°C and H_2O (11.1L) was added dropwise over 1 hr. The mixture was then reheated to gentle reflux for 1 hr, cooled to 25°C, and transferred to a separating funnel. H_2O (15L) and hexane (15L) were added and the phases separated. The lower layer was re-extracted with hexane (15L) and the combined organic extracts were washed successively with H_2O (2 x 10L) and sat. $NaHCO_3$ (15L) before being dried over Na_2SO_4, filtered and evaporated to dryness to give the title compound, 2.40kg.

Step C: Preparation of 5-formylbenzofuran

A slurry of powdered magnesium (11.44g) and iodine (0.12g) in THF (120mL) was heated to 50°C under a N_2 blanket for 0.5 hr. A 30mL portion of the material prepared above in Example 31, Step B (90g) in THF (225mL) was then added at 50°C, without stirring. This mixture was aged for 0.5 hr and then the remaining 195mL of the THF solution was added over 1.5 hr (with stirring) while maintaining a gentle reflux. When the addition was complete, the

mixture was aged at 50°C for 1 hr and then was cooled to 5°C before DMF (45mL) was added dropwise over 30 min while maintaining the reaction temperature between 5 - 10°C. The mixture was then aged at 10°C for 1 hr and then cooled to 5°C before a mixture of 3N HCl (300mL) and a 50% sat. solution of brine (225mL) was added while maintaining the reaction temperature below 15°C. The pH was also monitored and when the pH of the aqueous layer had fallen to 6, EtOAc (200mL) was added and the remaining 3N HCl / brine mixture was added (final pH approx. 1.2). This mixture was stirred for 1 hr and the aqueous layer was removed and extracted with EtOAc (150mL). The combined organic layers were washed successively with 2N HCl (100mL) and brine (3 x 80mL), dried over Na_2SO_4, filtered and evaporated to dryness to give 63.6g of the title compound as an orange oil that was of sufficient purity for use in the next step.

Step D: Preparation of (S)-1-(benzofuran-5-yl)-1-butanol

To a solution of (R,R)-di-(trifluoromethylsulfonyl)-1,2-diaminocyclohexane (1.92g) in dry toluene (80mL) at 23°C under a N_2 blanket was added titanium tetraisopropoxide (15mL) and the slurry was warmed to 40°C for 20 min, and then was cooled to 0°C. In a separate vessel di-n-propylzinc (52mL) was mixed with dry hexane (400mL) and the resulting homogeneous solution was added to the solution prepared above while maintaining the temperature between -5 - 0°C. This mixture, at 0°C, was then added to a solution of the material prepared above in Example 31, Step C (40g) in toluene (150mL) over 30

min. The resulting yellow mixture was then stirred at 0°C for 18 hr and then was cooled to -5°C and quenched by the addition of 2N HCl (500mL) over 1.5 hr, while maintaining the reaction temperature between -5 -0°C. The resulting two phase mixture was stirred at 0°C for 1.2 hr and EtOAc (100mL) was added. The aqueous layer was removed and extracted with EtOAc (150mL). The combined organic layers were washed successively with 2N HCl (100mL) and brine (2 x 150mL) and then were dried over Na_2SO_4, filtered and evaporated to dryness to afford 50g of a yellow oil which solidifed on standing. The optical purity of this material is 95.5%-ee.

Step E: Preparation of (R)-1-amino-1-(benzofuran-5-yl)-butane

To a solution of triphenylphosphine (132.3g) in THF (960mL) at 0°C was added ethyl azodicarboxylate (79.2mL). The resulting solution was stirred at 0°C until a thick slurry was obtained and then diphenylphosphoryl azide (54.2mL) was added. To this mixture was added a solution of the material prepared above in Example 31, Step D (47.7g) in THF (125mL) over a 1.5 hr time period while maintaining the reaction temperature between -3 - -2°C, and the resulting homogeneous solution was stirred at 0°C for 0.5 hr. To this mixture was added triphenylphosphine (96.2g) and the solution was allowed to warm to 23°C over 1 hr and then was heated at 50°C for 2.5 hr. 20% Aqueous NaOH (580mL) was then added to the mixture which was stirred at 50°C for an additional 1 hr. The two phases mixture was cooled to 23°C and the lower aqueous layer was separated and extracted

with THF (300mL). The combined organic layers were washed with brine (2 x 500mL) and then concentrated in vacuo to give 460g of an orange oil which was dissolved in t-butylmethyl ether (1L) and allowed to stand for 18 hr. The solid which formed was filtered off and washed with t-butylmethyl ether (100mL) and the filtrate was concentrated to dryness to afford 302g of an orange oil which was purified by silica gel chromatography (1.5kg column developed successively with hexane:EtOAc (1:1, 8L), EtOAc (4L) and then EtOAc containing 1% Et_3N). Fractions containing the required product (and triphenylphosphine oxide) were pooled and evaporated to dryness. The oily residue so obtained was swished with hexane:EtOAc (5:1, 200mL) and filtered. The filtrate was concentrated in vacuo to afford 35.3g of an oil which was dissolved in EtOAc (80mL) and washed with 2N HCl (2 x 45mL). The pooled aqueous layers were cooled to 5°C and treated with 50% NaOH (20mL) before being extracted with Et_2O (2 x 50mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to afford 20.3g of the title compound as an orange oil with an optical purity of 88% ee.

Step F: Preparation of (R)-5-[(1-isocyanate)butan-1-yl]benzofuran

To a solution of the material prepared above in Example 31, Step E (19.2g) in toluene (192mL) was added conc. HCl (12.7mL) dropwise, while maintaining the reaction temperature between 20 - 25°C. The white viscous slurry was stirred for 30 min at 20°C and then toluene (200mL) was added and the slurry was

heated at reflux with the azeotropic removal of water. The dried slurry was then cooled to 100°C and a solution of phosgene in toluene (1.93M, 150mL) was added slowly over 1 hr. Complete solution was obtained after 1 additional hr. This solution was cooled to 10°C and sat. $NaHCO_3$ (200mL) was added followed by EtOAc (300mL). The organic layer was separated and washed successively with sat. $NaHCO_3$ (200mL) and brine (200mL) and then dried over Na_2SO_4, filtered and evaporated to dryness to give the title compound (21.5g) as an orange oil suitable for use in the next step.

EXAMPLE 32

(4S)-3,3-Diethyl-1-[[(R)-1-(benzofuran-5-yl)butyl-amino]carbonyl]-4-[4-(carboxymethyl)phenoxy]-azetidin-2-one

Method A:

Step A: Preparation of ethyl 4-[(2,2-diethoxy)-ethoxy]phenylacetate

To a solution of 4-hydroxyphenylacetic acid (50.0 gm, 0.33 mol) in DMSO (300 mL) was added 50% aqueous NaOH (57.0 gm, 0.71 mol) with stirring. After stirring for 10 min at room temperature bromoacetaldehyde diethyl acetal (66.0 gm, 0.33 mol) was added. The solution was heated at 100-110°C for 2 hr when an additional 2 gm of 50% NaOH was added. After heating for another hour the reaction mixture was cooled and poured into a mixture of aqueous HCl (30 mL of conc. HCl in 400 mL ice-H_2O) and Et_2O. The layers were separated and hexane was added to the Et_2O layer. The organic layer was washed

successively with H_2O (twice) and saturated NaCl before being dried over Na_2SO_4, filtered and evaporated to dryness to give 83.7 gm (0.31 mol) of 4-[(2,2-diethoxy)ethoxy]phenylacetic acid which was suitable for use in the next step.
NMR ($CDCl_3$), δ from TMS: 1.25 (t, 6H, J = 7Hz), 3.56 - 3.90 (m, 4H), 3.61 (s, 2H), 4.03 (d, 2H, J = 7Hz), 4.86 (t, 1H, J = 7Hz), 6.91 (d, 2H, J = 8Hz), 7.21 (d, 2H, J = 8Hz).

The residue prepared above was dissolved in EtOH (500 mL) containing conc. H_2SO_4 (1 mL) and the solution was heated under reflux for 6 hr. The reaction mixture was then cooled, concentrated to 300 mL and this solution was partitioned between H_2O and Et_2O. The aqueous layer was extracted with Et_2O and the pooled organic layers were washed successively with H_2O, sat. $NaHCO_3$, and sat. NaCl before being dried over Na_2SO_4, filtered and evaporated to dryness to give 86.0 gm (0.29 mol), of the title compound.
NMR ($CDCl_3$), δ from TMS: 1.25 (t, 9H, J = 7Hz), 3.55 - 3.90 (m, 4H), 3.56 (s, 2H), 4.02 (d, 2H, J = 7Hz), 4.16 (q, 2H, J = 7Hz), 4.86 (t, 1H, J = 7Hz), 6.89 (d, 2H, J = 8Hz), 7.20 (d, 2H, J = 8Hz).

Step B: Preparation of ethyl benzofuran-5-ylacetate

In a 1 L 3-necked flask equipped with a mechanical stirrer and a condenser was added polyphosphoric acid (80 gm) and benzene (450 mL). This mixture was heated to reflux for 15 min and then ethyl 4-[(2,2-diethoxy)ethoxy]phenylacetate (86 gm, 0.29 mol) in benzene (50 mL) was added and the reflux was continued for 40 min. The reaction mixture was cooled and the mobile phase was decanted off. This

benzene solution was washed successively with H_2O, sat. $NaHCO_3$, and sat. NaCl before being dried over Na_2SO_4, filtered and evaporated to dryness. This residue was dissolved in 10-15% EtOAc in hexane and passed through a short silica gel column (5 cm x 10 cm dia.) in the same solvent. The eluent was evaporated to dryness to give a yellow liquid which was further purified by preparative LC using 10% EtOAc in hexane as eluent to give 17.4 gm of ethyl benzofuran-5-ylacetate.

NMR ($CDCl_3$), δ from TMS: 1.26 (t, 3H, J = 7Hz), 3.70 (s, 2H), 4.19 (q, 2H, J = 7Hz), 6.75 (m, 1H), 7.2 - 7.7 (m, 4H).

Step C: Preparation of (R,S)-α-Allylbenzofuran-5-ylacetic acid

Ethyl benzofuran-5-ylacetate (17.42 gm, 0.085 mol) was dissolved in dry THF (120 mL) and the solution was cooled under a nitrogen blanket in a dry ice bath. After 10 min, a solution of 1 M lithium bis(trimethylsilyl)amide in THF (90 mL) was added via an addition funnel over a 15 min time period. After stirring for 15 min, allyl bromide (7.9 mL, 11.04 gm, 0.091 mol) was added and the stirred solution was allowed to rise to room temperature over 1 hr. The solution was poured into ice-H_2O containing 20 mL of 1.2N HCl and extracted with Et_2O. The organic layer was washed successively with 1.2N HCl and sat. NaCl before being dried over Na_2SO_4, filtered and evaporated to dryness to give 21.6 gm of crude ethyl (R,S)-α-allylbenzofuran-5-ylacetate.

The ethyl (R,S)-α-allylbenzofuran-5-ylacetate obtained above was dissolved in EtOH (200

mL) and treated with H_2O (30 mL) and 5N NaOH (30 mL). This solution was heated at 60°C for 1.5 hr, stirred overnight at room temperature and then heated at 60°C for an additional 1 hr before being worked up. The reaction mixture was cooled and poured into ice-H_2O (400 mL) containing conc. HCl (14 mL) and Et_2O. The layers were separated and the aqueous layer was further extracted with Et_2O. The pooled Et_2O layers were washed successively with H_2O and sat. NaCl, dried over Na_2SO_4, filtered and evaporated to dryness to give 16.88 gm of (R,S)-α-allylbenzofuran-5- ylacetic acid which solidified on standing. NMR ($CDCl_3$), δ from TMS: 2.58 (m, 1H), 2.84 (m, 1H), 3.72 (m, 1H), 5.00 - 5.20 (m, 2H), 5.64 - 5.84 (m, 1H), 6.74 (m, 1H), 7.20 - 7.70 (m, 4H).

Step D: Preparation of (R)-α-allylbenzofuran-5-ylacetic acid, (R)-(+)-α-methylbenzylamine salt

To a solution of the racemate prepared above in Example 32, Method A, Step C (39.43 gm, 0.18 mol) in iPrOH (285 mL) was added (R)-α-methylbenzylamine (14.4 gm, 0.12 mol). A solid formed immediately and the mixture was allowed to stand at room temperature for 1 hr. The solid was filtered off, washed with cold iPrOH and dried. This solid (α_D = -4.55) was recrystallized from iPrOH (750 mL) to give 26.9 gm of material with α_D = -14.1. An additional recrystallization from iPrOH (800 mL) gave 20.3 gm (0.06 mol) of product with α_D = -22.61 which was suitable for use in the next step.

Note that the mother liquors from these crystallizations can be racemized (via conversion to

the free acid and esterification, followed by successive treatments with lithium bis(trimethylsilyl)amide, acetic acid and then de-esterification with NaOH in MeOH) and then resolution of this material can be realized as described above. In this fashion the bulk of the racemate can be converted into the required enantiomer.

Step E: Preparation of (R)-α-allylbenzofuran-5-yl-methyl isocyanate

The material prepared above in Example 32, Method A, Step D (20.3 gm, 0.06 mol) was added to 2N HCl (35 mL) in a mixture of ice-H_2O (150 mL) and Et_2O (150 mL). This mixture was stirred for a few minutes until the solid dissolved and the layers were then separated and the aqueous layer was extracted with Et_2O. The Et_2O layer was washed with sat. NaCl, dried over Na_2SO_4, filtered and evaporated to dryness. The residue so obtained was dissolved in CH_2Cl_2 (200 mL) and 25 drops of DMF were added. This solution was cooled in an ice bath and a solution of oxalyl chloride (5.5 mL, 0.063 mol) in CH_2Cl_2 (20 mL) was added over a 10 min period. The reaction mixture was stirred for 1 hr (gas evolution stopped after approximately 45 min) and then was evaporated to dryness. The residue so obtained was dissolved in acetone (120 mL) and the solution was added to a cooled (ice bath) solution of NaN_3 (4.11 gm, 0.063 mol) in H_2O (80 mL) while maintaining the temperature between 2-5°C. After the addition was completed, the reaction was stirred for 30 min and then poured into a mixture of ice-H_2O/$CHCl_3$. The layers were

separated and the aqueous layer was extracted with $CHCl_3$. The pooled organic layers were washed with cold H_2O and sat. NaCl before being dried over Na_2SO_4, filtered and concentrated to 250 mL. This solution was heated in an oil bath at 60°C for 30 min (gas evolution ceased) and then was evaporated to dryness. The residue so obtained was dried by azeotropic concentration from a benzene solution (150 mL) and then was stored in the freezer overnight as a benzene solution before being used in the next step. Upon evaporation to dryness, this solution contained 12.8 gm (0.06 mol) of product.

Step F: Preparation of (4S)-3,3-diethyl-1-[{(R)-1-(benzofuran-5-yl)-but-3-enylaminocarbonyl]-4-[4-(allyloxycarbonylmethyl)phenoxy]azetidin-2-one

(R)-α-Allylbenzofuran-5-ylmethyl isocyanate (8.52 gm, 0.04 mol), prepared as described above in Step E, was added to a solution of (S)-3,3-diethyl-4-[(4-allyloxy-carbonylmethyl)phenoxy]azetidin-2-one (11.33 gm, 0.035 mol, prepared as described in Example 30) in DMF (70 mL) and powdered K_2CO_3 (0.97 gm) was added. This mixture was stirred vigorously to give 13.9 gm (0.026 mol) of the required product. NMR ($CDCl_3$), δ from TMS: 0.95 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz), 1.7 - 2.1 (m, 4H), 2.63 (t, 3H, J = 7Hz), 3.59 (s, 2H), 4.58 (d of t, 2H, J = 6Hz, J = 1Hz), 5.04 - 5.32 (m, 5H), 5.57 (s, 2H), 5.57 - 6.06 (m, 2H), 6.74 (d of d, 1H, J = 2Hz, J = 1Hz), 7.1 - 7.56 (m, 8H), 7.61 (d, 1H, J = 2Hz)

Step G: Preparation of (4S)-3,3-diethyl-1-[{(R)-1-(benzofuran-5-yl)-but-3-enylaminocarbonyl]-4-[4-(carboxymethyl)phenoxy]azetidin-2-one

To a solution of (4S)-3,3-diethyl-1-[{(R)-1-(benzofuran-5-yl)-but-3-enylaminocarbonyl]-4-[4-(allyloxycarbonylmethyl)phenoxy]azetidin-2-one (15.04 gm, 0.028 mol) in EtOAc (250 mL) was added triphenylphosphine (0.5 gm, 0.002 mol) and acetic acid (10 mL). The solution was degassed and maintained under an atmosphere of nitrogen. Tetrakis(triphenylphosphine)palladium(0) (0.5 gm, 0.00043 mol) was then added and the reaction mixture was stirred for 3 hr and then an additional 10 mL of acetic acid was added. After stirring for a total of 6.5 hr, the reaction was diluted with Et_2O and the mixture was extracted with H_2O (twice) and sat. NaCl. The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness to give 17.9 gm of crude product as an oil which was suitable for use in the next step.

NMR ($CDCl_3$), δ from TMS: 0.95 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz), 1.7 - 2.1 (m, 4H), 2.63 (t, 2H, J = 7Hz), 3.59 (s, 2H), 5.04 - 5.30 (m, 3H), 5.58 (s, 1H), 5.58 - 5.90 (m, 1H), 6.74 (d of d, 1H, J = 2Hz J = 1Hz), 7.10 - 7.56 (m, 8H), 7.60 (d, 1H, J = 2Hz).

Step H: Preparation of (4S)-3,3-diethyl-1-[[(R)-1-(benzofuran-5-yl)butylamino]carbonyl]-4-[4-(carboxymethyl)phenoxy]azetidin-2-one

The crude (4S)-3,3-diethyl-1-[{(R)-1-(benzofuran-5-yl)-but-3-enylaminocarbonyl]-4-[4-(carboxymethyl)phenoxy]azetidin-2-one prepared as described above in Example 32, Method A, Step G (17.9

gm) was dissolved in EtOAc (60 mL) and diluted with abs. EtOH (110 mL). This solution was hydrogenated for 30 min on a Parr shaker in three portions using 5% Pd on C as catalyst (0.5 g in each portion). Hydrogen uptake was slow, and after 5 min, 0.15 gm of 10% Pd on C was added to each portion. After an additional 25 min, the reactions were pooled, filtered, and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc (20 mL)-EtOH (80 mL), divided into two equal portions, 10% Pd on C (0.15 gm) was added to each, and the hydrogenation was continued for 15 min. The reaction mixture was then filtered, washed with EtOAc and evaporated to dryness. This residue was then purified by preparative LC to give 11.03 gm (0.022 mol) of the required product as a stiff clear foam. NMR ($CDCl_3$), δ from TMS: 0.92 (t, 3H, J = 7Hz), 0.93 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz), 1.33 (m, 2H), 1.7 - 2.1 (m, 6H), 3.59 (s, 2H), 4.95 (q, 1H, J = 8Hz), 5.58 (s, 1H), 6.74 (d of d, 1H, J = 1Hz, J = 2Hz), 7.0 - 7.54 (m, 8H), 7.61 (d, 1H, J = 2Hz).

Step I: Preparation of (4S)-3,3-diethyl-1-[[(R)-1-(benzofuran-5-yl)butylamino]carbonyl]-4-[4-(carboxymethyl)phenoxy]azetidin-2-one, potassium salt

A solution of the free acid (7.01 gm 0.014 mol), prepared as described above in Example 32, Method A, Step H in H_2O (100 mL) was treated with a solution of $KHCO_3$ (1.424 gm, 0.014 mol) in H_2O (100 mL). Warming of the mixture and the addition of MeOH (20 mL) was required to obtain a homogeneous milky solution. This was filtered and the filtrate was

concentrated to 150 mL, diluted with H_2O (100 mL) and then lyophilized to give the required product as a hygroscopic white solid which analysed as a hydrate. Optical rotation α_D (c = 0.49, MeOH) = +55.31;
Anal. Calc. for $C_{28}H_{31}N_2O_6K_2.75H_2O$ (580.21);
C, 57.96, H, 6.34, N, 4.83,
Found; C, 57.94, H, 6.10, N, 4.68

Method B:

Step A: Preparation of p-methoxybenzyl bromide

p-Methoxybenzyl alcohol (13.8 g, 0.1 mol) was added dropwise to a solution of 48% HBr (50 gm, 0.3 mol of HBr) over a period of 15 min and the solution was then stirred for an additional 15 min before being poured into a mixture of ice-H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O. The combined Et_2O extracts were washed with sat. NaCl, dried over Na_2SO_4 and evaporated to dryness to give 23.4 gm of p-methoxybenzyl bromide suitable for use in the next step.
NMR ($CDCl_3$), δ from TMS: 3.80 (s, 3H), 4.49 (s, 2H), 6.86 (d, 2H, J = 8Hz), 7.32 (d, 2H, J = 8Hz).

Step B: Preparation of (S)-3,3-diethyl-4-[4-({p-methoxybenzyloxycarbonylmethyl)phenoxy]-azetidin-2-one

(S)-3,3-Diethyl-4-[4-(carboxymethyl)-phenoxy]azetidin-2-one, (S)-(-)-α-methylbenzylamine salt (31.8 gm, 0.08 mol) was added to a mixture of H_2O, 2N HCl, and Et_2O and was mixed thoroughly until dissolution occured. The layers were separated and

the organic layer was washed successively with H_2O and sat. NaCl, before being dried over Na_2SO_4, filtered and evaporated to dryness. This residue was dissolved in DMF (100 mL) and powdered K_2CO_3 (11.81 gm, 0.085 mol) was added. After 5 min, p-methoxybenzyl bromide (23.4 gm, 0.08 mol) in DMF (20 mL) was added and the solution was stirred at room temperature overnight and then poured into a mixture of H_2O and Et_2O. The layers were separated and the organic layer was washed successively with H_2O (twice), and sat. NaCl before being dried over Na_2SO_4, filtered and evaporated to dryness to give 32.82 gm of (S)-3,3-diethyl-4-[4-({p-methoxybenzyloxycarbonylmethyl)phenoxy]azetidin-2-one as a yellow oil suitable for use without further purification.

NMR ($CDCl_3$), δ from TMS: 1.03 (t, 3H, J = 7Hz), 1.06 (t, 3H, J = 7Hz), 1.65 - 2.05 (m, 4H), 3.59 (s, 2H), 3.80 (s, 3H), 5.05 (s, 2H), 5.53 (s, 1H), 6.65 (br s, 1H), 6.80 - 7.40 (m, 8H).

Step C: Preparation of (4S)-3,3-diethyl-1-[{(R)-1-(benzofuran-5-yl)-but-3-enylaminocarbonyl]-4-[4-({p-methoxybenzyloxycarbonylmethyl)-phenoxy]azetidin-2-one

(R)-α-Allylbenzofuran-5-ylmethyl isocyanate (12.8 gm, 0.06 mol), prepared as described in Example 32, Method A, Step E was dissolved in DMF (50 mL) and a solution of (4S)-3,3-diethyl-4-[4-({p-methoxybenzyl-oxycarbonylmethyl)phenoxy]azetidin-2-one, prepared as described above in Example 32, Method B, Step B (19.85 gm, 0.05 mol) in DMF (50 mL) was added. Powdered K_2CO_3 (1.39 gm) was added and the mixture

was vigorously stirred for 2 hr at room temperature. The reaction mixture was then partitioned between Et_2O and H_2O and the aqueous layer was further extracted with Et_2O. The pooled organic layers were washed successively with H_2O (twice) and sat. NaCl before being dried over Na_2SO_4, filtered and evaporated to dryness. This residue so obtained was purified in two batches on preparative LC, using 25-50% EtOAc in hexane as eluent, to give 20.3 gm (0.033 mol) of the desired product.
NMR ($CDCl_3$), δ from TMS: 0.95 (t, 3H, J = 7Hz), 1.08 (t, 3H, J = 7Hz), 1.65 - 2.05 (m, 4H), 2.63 (t, 2H, J = 7Hz), 3.58 (s, 2H), 3.81 (s, 3H), 5.00 - 5.22 (m, 3H), 5.05 (s, 2H), 5.58 (s, 1H), 5.60 - 5.80 (m, 1H), 6.70 - 7.70 (m, 14H).

Step D: Preparation of (4S)-3,3-diethyl-1-[{(R)-1-(benzofuran-5-yl)butylaminocarbonyl]-4-[4-({p-methoxybenzyloxycarbonylmethyl)phenoxy]-azetidin-2-one

The (4S)-3,3-diethyl-1-[{(R)-1-(benzofuran-5-yl)-but-3-enylaminocarbonyl]-4-[4-({p-methoxybenzyloxycarbonylmethyl)phenoxy]azetidin-2-one prepared as described above in Example 32, Method B, Step C (20.3 gm, 0.033 mol) was dissolved in EtOAc (50 mL) and EtOH (150 mL). This solution was divided into four equal portions and each was hydrogenated at <35 psi using 5% Pd/C (0.5 gm) in a Parr apparatus. The hydrogenation was stopped after initial hydrogen absorption had stopped (3.5 - 4 min) and the catalyst was removed by filtration and washed with EtOAc. The filtrates from the four runs were pooled and evaporated to dryness to give 19.0 gm (0.031 mol) of

the required product which was suitable for use in the next step without further purification.
NMR ($CDCl_3$), δ from TMS: 0.92 (t, 3H, J = 7Hz), 0.94 (t, 3H, J = 7Hz), 1.08 (t, 3H, J = 7Hz), 1.30 (m, 2H), 1.65 - 2.10 (m, 6H), 3.59 (s, 2H), 3.81 (s, 3H), 4.97 (q, 1H, J = 7Hz), 5.06 (s, 2H), 5.58 (s, 1H), 6.70 - 7.70 (m, 14H).

Step E: Preparation of (4S)-3,3-Diethyl-1-[[(R)-1-(benzofuran-5-yl)butylamino]carbonyl]-4-[4-(carboxymethyl)phenoxy]azetidin-2-one

The (4S)-3,3-diethyl-1-[{(R)-1-(benzofuran-5-yl)butylaminocarbonyl]-4-[4-({p-methoxybenzyloxy-carbonylmethyl)phenoxy]azetidin-2-one prepared as described above in Example 32, Method B, Step D (13.53 gm, 0.022 mol) was dissolved in anisole (15 mL) and the solution was cooled in an ice bath for 15 min. This chilled solution was then divided into three portions and to each was added ice cold CF_3CO_2H (20 mL). After 10 min at ice bath temperature, dichloroethane (50 mL) was added to each portion and the solutions were rapidly evaporated to dryness (bath temperature <30°C) and the residues were diluted with Et_2O and poured into ice-H_2O. The layers were separated and the aqueous layer was extracted with Et_2O. The Et_2O layers from the three reactions were pooled and washed successively with cold H_2O and sat. NaCl before being dried over Na_2SO_4, filtered and evaporated to dryness. This residue was purified by preparative LC to give 6.68 gm (0.014 mol) of the required product as a thick oil. This material was identical in all respects to that prepared via Method A.

Method C:

Step A: Preparation of methyl benzofuran-5-ylacetate

4-Hydroxyphenylacetic acid (20 gm, 0.13 mol) was dissolved in DMF (50 ml) and then slowly added to washed NaH (0.26 mol) in DMF (100 ml). Bromoacetaldehyde diethyl acetal (29 ml, 0.195 mol) was then added and the mixture was heated at 160°C (oil bath) for 3 hr. The mixture was cooled, water was added and the mixture was rendered basic by the addition of 2N NaOH. The solution was heated to 80°C for 1 hr and then was cooled and extracted twice with Et_2O, acidified to pH 3 and then extracted twice more with Et_2O. The second Et_2O extracts were pooled, dried and evaporated to dryness. This residue was purified by preparative LC to give 8 gm of a pure oil which was dissolved in Et_2O and 120 ml of a CH_2N_2 solution was added (slight molar excess). Upon completion of the esterification, the excess CH_2N_2 was destroyed by the addition of acetic acid and the mixture was evaprated to an oil. This was dissolved in benzene (100 ml) and polyphosphoric acid (5 gm) was added and the mixture was heated at 90-100°C with good mechanical stirring for 3 hr. The mixture was decanted and evaporated to dryness and the residue was purified by flash chromatography to give 1.3 gm of the title compound as an oil.

NMR ($CDCl_3$): δ 3.58-3.83 (m, 5H), 6.74 (d of d, 1H), 7.18 - 7.54 (m's, 5H), 7.62 (d, 1H)

Step B: Preparation of benzofuran-5-ylacetic acid

1.20 gm (6.3 mmol) of material prepared as described in Step A above was treated with 2N NaOH

(6.5 ml) and MeOH (10 ml) at room temperature for 3 hr. The reaction mixture was then diluted with H_2O and the resultant solution was washed with Et_2O. The aqueous layer was acidified and extracted twice with EtOAc. The combined EtOAc layers were dried over Na_2SO_4, filtered and evaporated to dryness to give 1.1 gm (6.25 mmol) of the title compound suitable for direct use in the next step.

Step C: Preparation of (R)-α-allyl-benzofuran-5-ylacetic acid, (R)-(+)-α-methylbenzylamine salt (alternate route to that described in Example 32 Method A, Step D

10.0 gm (56.76 mmol) of material prepared as described in Step B above was dissolved in THF (300 ml) and added dropwise over 15 min to a cold (-5 to -10°C) solution of lithium diisopropylamine [prepared from diisopropylamine (20.45 ml, 141.88 mmol) and 2.5M n-BuLi (48 ml, 120 mmol)] in THF. The reaction mixture was stirred at -10°C for 30 min and then a solution of allyl bromide (10.81 ml, 113.52 mmol) in THF (20 ml) was added quickly. This mixture was stirred at -10°C for 30 min and then cooled and added to a mixture of ice-H_2O (900 ml), 2N HCl (300 ml) and Et_2O (500 ml). After stirring for 5 min the layers were separated and the aqueous layer was washed with Et_2O (100 ml) and the pooled organic layers were washed successively with aqueous $NaHSO_3$ and brine and then dried over Na_2SO_4, filtered and evaporated to dryness. The orange-yellow oil so obtained was dissolved in isopropanol (255 ml) and (R)-(+)-α-methylbenzylamine (5.43 ml, 42.57 mmol) was added, with stirring. Any solids which formed were

redissolved by heating and and the solution was allowed to cool in the freezer overnight. Several recrystallizations from isopropanol gave the title compound (7.19 gm) as a white solid which was identical to material prepared in Example 32, Method A, Step D.

Step D: Preparation of (R)-α-allyl-benzofuran-5-ylmethyl isocyanate

This was prepared as described in Example 32, Method A, Step E.

Step E: Preparation of (4S)-3,3-diethyl-1-[[(R)-1-(5-benzofuran-5-yl)-but-3-enylamino]-carbonyl]-4-[(4-t-butoxycarbonylmethyl) phenoxy]azetidin-2-one

A solution of the material prepared in Step D above (470 mg, 2.2 mmol) and the material prepared in Example 22 (600 mg, 1.8 mmol) in Et_3N (0.38 ml, 2.7 mmol), DMAP (5 mg) and CH_2Cl_2 (5 ml) was stirred overnight at room temperature and then was heated at 40-50°C. The reaction mixture was evaporated to dryness and the residue was purified by repeated chromatography to give 350 mg of the title compound (higher Rf isomer).

NMR ($CDCl_3$): δ 0.92 (2t's, 6H), 1.08 (t, 3H), 1.34 (m, 2H), 1.43 (s, 9H), 1.68 - 2.1 (m, 6H), 3.46 (s, 2H), 4.95 (q, 1H), 5.55 (s, 1H), 6.74 (m, 1H), 6.96 - 7.56 (m's, 8H), 7.61 (d, 1H)

The lower R_f isomer, (4R)-3,3-diethyl-1-[(R)-α-allyl-(5-benzofuranyl)methylaminocarbonyl]-4-[(4-t-butoxycarbonylmethyl)phenoxy]azetidin-2-one, was also obtained, 400 mg.

Step F: Preparation of (4S)-3,3-diethyl-1-[(R)-1-(benzofuran-5-yl)butylamino]carbonyl]-4-[(4-carboxymethyl)phenoxy]azetidin-2-one

The higher Rf isomer (350 mg) prepared as described above in Step D was dissolved in EtOAc (10 ml) and 5% Pd/C (50 mg) was added. This mixture was hydrogenated at 20 p.s.i. for 8 min, when tlc and NMR indicated complete reduction of the allyl group. The reaction was filtered and the filtrate was evaporated to dryness. The residue so obtained was dissolved in a mixture of cold CF_3CO_2H (5 ml) and anisole (1 ml) and the reaction was stored at 0°C for 20 min before being evaporated to dryness. This crude product was purified by chromatography on thick layer silica gel plates developed with EtOAc/hexane/HOAc (35:64:1) to give 200 mg of the title compound.
NMR ($CDCl_3$): δ 0.92 (t, 3H), 0.94 (t, 3H), 1.04 (t, 3H), 1.34 (m, 2H), 1.68-2.10 (m, 6H), 3.58 (s, 2H), 4.95 (q, 1H), 5.57 (s, 1H), 6.74 (d of d, 1H), 6.98-7.54 (m, 8H), 7.61 (d, 1H)

Method D:

Step A Preparation of (4S)-3,3-diethyl-1-[[(R)-1-(5-benzofuran-5-yl)-butyl-1-amino]carbonyl]-4-[(4-allyloxycarbonylmethyl)phenoxy]-azetidin-2-one

To a solution of the material prepared above in Example 31, Step F (19.0g) in DMF (50mL) at room temperature was added a solution of the material prepared in Example 30, Method B (26.5g), also in DMF (100mL). K_2CO_3 (1.22g) was added and the slurry so obtained was stirred for 1 hr. The reaction mixture

was then partitioned between EtOAc (250mL) and 2N HCl (100mL) and the the organic layer was washed successively with 2N HCl (100mL), 0.1N HCl (2 x 100mL) and brine (2 x 100mL) before being evaporated to dryness to give 52.8g of the title product (de = 85%).

Step B: Preparation of (4S)-3,3-diethyl-1-[[(R)-1-(5-benzofuran-5-yl)-butyl-1-amino]carbonyl]-4-[(4-carboxymethyl)phenoxy]-azetidin-2-one, tris (hydroxymethyl)aminomethane salt

To a solution of the material prepared above in Example 32, Method D, Step A (10.0g) in DMF (150mL) at 20°C under a N_2 blanket was added 10% Pd on carbon (2.0g), followed by a 55% solution of ammonium formate in H_2O (15.0mL). This mixture was heated at 45°C for 30 min and then was cooled to 20°C and filtered (washing the pad with 30mL of DMF). The filtrate was partitioned between 1N HCl (100mL) and EtOAc (200mL) and the organic layer was washed successively with 0.1N HCl (2 x 100mL) and brine (2 x 100mL) before being evaporated to dryness to give the title compound (free acid) as a pale yellow viscous gum (9.25g).

A slurry of the free acid prepared as described above (39.0g) and tris-(hydroxymethyl)aminomethane (9.6g) in isopropanol (500mL) was warmed to 60°C to ensure dissolution. Hexanes (1.3L) was then added dropwise until a slightly cloudy mixture was obtained. This mixture was seeded (200mg) and allowed to cool to 20°C overnight. Hexanes (700mL) were then added and the slurry was aged at 5°C for 2 hr and the solid so formed was filtered, washed with

isopropanol/hexanes (1:4; 80mL) and then dried in vacuo at 20°C to give the title compound (29.9g).

EXAMPLE 33

(4S)-3,3-Diethyl-1-[(R-α-n-propyl-(4-methyl)-benzylaminocarbonyl-4-[(4-carboxy-3-methyl)-phenoxy]azetidin-2-one

Step A: Preparation of 4-hydroxy-2-methylbenzoic acid

4'-Hydroxy-2'-methylacetophenone (15 gm, 0.1 mol) was dissolved in pyridine and iodine (25.4 gm) was added. This mixture was heated to 100°C for 1 hr and then allowed to stand at room temperature overnight. A thick precipitate was obtained and the mixture was diluted with Et_2O before filtering. The solid so obtained was added to 5N NaOH (200 ml) and heated on the steam bath for 1 hr before being cooled and acidified with HCl. This mixture was extracted twice with Et_2O and the pooled organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was crystallized from Et_2O - hexane to give 9.8 gm of the title compound as a solid.

Step B: Preparation of benzyl 4-hydroxy-2-methyl-benzoate

9.5 gm (63 mmol) of material prepared as described in Step A above was dissolved in DMF (100 ml) and benzyl bromide (8.4 ml, 69.3 mmol) was added followed by powdered K_2CO_3 (13 gm, 94 mmol). This mixture was stirred at 60°C for 2 hr and then was cooled, diluted with Et_2O and poured onto ice chilled aq. HCl. The layers were separated and the aqueous

layer was extracted twice more with Et_2O. The pooled organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. This crude product was purified by flash chromatography (silica gel, using 10% - 30% EtOAc in hexane as eluant) to give the title compound as an oil which upon trituration with hexane and cooling gave 8.5 gm of a white solid.

Step C: Preparation of (R,S)-3,3-diethyl-4-[(3-methyl-4-benzyloxycarbonyl)-phenoxy]azetidin-2-one

4-Propionyloxy-3,3-diethylazetidin-2-one (6.2 gm, 31 mmol, prepared in an analogous fashion as described in Example 22, Step B) was dissolved in toluene (100 ml) and material prepared as described in Step B above (5.0 gm, 21 mmol) was added followed by powdered $Ba(OH)_2.8H_2O$ (6.7 gm, 31 mmol). This mixture was heated at 50 - 60°C for 3 hr and then poured into ice-chilled 2N HCl. The mixture was extracted twice with Et_2O and the pooled organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. This residue was purified by flash chromatography (silica gel, using 20% - 40% EtOAc in hexane as eluant) to give 5.3 gm of the title compound as a a white solid.

Step D: Preparation of (4S)-3,3-diethyl-1-[(R)-α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4-carboxy-3-methyl)phenoxy]azetidin-2-one

A solution of the material prepared in Step C above (2.5 gm, 6.8 mmol) and the material prepared as in Example 28, Method B, Step B (2.0 gm, 10.2

mmol) in Et_3N (1.5 ml, 10.2 mmol) and CH_2Cl_2 (5 ml) was stirred at 50 - 60°C for 20 hr and then overnight at room temperature. The reaction mixture was then cooled and added to dilute HCl. The mix was extracted twice with Et_2O and the pooled organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography (silica gel, using 10% - 20% EtOAc in hexanes as eluant) to give 150 mg of pure (4S)-3,3-diethyl-1-[(R)-α-allyl-(4-methyl)-benzyl-aminocarbonyl-4-[(4-benzyloxycarbonyl-3-methyl)phenoxy]azetidin-2-one. Additional pure material was obtained by repeated chromatography of overlapping fractions. 650 mg of this pure material was dissolved in EtOH (10 ml) and hydrogenated for 2 hr at 40 p.s.i. using 100mg of 10% Pd/C as catalyst. The reaction was filtered and evaporated to dryness to give 500 mg of the title compound as a pure foam. NMR ($CDCl_3$): δ 0.91 (t, 3H), 0.96 (t, 3H), 1.06 (t, 3H), 1.30 (m, 2H), 1.6-2.1 (m, 6H), 2.31 (s, 3H), 2.60 (s, 3H), 4.83 (q, 2H), 5.70 (s, 1H), 6.92 (d, 1H), 6.98-7.22 (m, 6H), 7.99 (d, 1H)

EXAMPLE 34

(4S)-3,3-Diethyl-1-[(R)-α-n-propyl-(4-methyl)benzyl-aminocarbonyl]-4-[(4-carboxy-3-chloro)phenoxy]-azetidin-2-one

Starting with 4-propionyloxy-3,3-diethyl-azetidin-2-one (prepared in an analogous fashion as described in Example 22, Step B and as shown in Scheme (d)), followed by displacement with benzyl 2-chloro-4-hydroxybenzoate (prepared from 2-chloro-4-hydroxybenzoic acid in a fashion analogous to that

described in Example 23, for benzyl 4-hydroxy-phenyl acetate) as described in Example 24, Method A, Step C and acylation of the nitrogen with the isocyanate prepared as described in Example 28, followed by catalytic reduction and deblocking gave the title compound.

NMR ($CDCl_3$): δ 0.9 (t, 3H), 0.97 (t, 3H), 1.05 (t, 3H), 1.31 (m, 2H), 1.7-2.1 (m, 6H), 2.33 (3, 3H), 4.82 (q, 1H), 5.68 (s, 1H), 6.90 (d, 1H), 7.1-7.4 (m, 6H), 7.98 (d, 1H)

EXAMPLE 35

(4S)-3,3-Diethyl-1-[(R)-α-n-propyl-(4-methyl)benzyl-aminocarbonyl]-4-[(4-carboxy-3-fluoro)phenoxy]-azetidin-2-one

This was prepared as described above in Example 33 except that benzyl 2-fluoro-4-hydroxy-benzoate (prepared from 2-fluoro-4-nitrotoluene by oxidation with $KMnO_4$ to give 2-fluoro-4-nitrobenzoic acid, followed by catalytic reduction to give 4-amino-2-fluorobenzoic acid, followed by diazotization/hydrolysis to give 4-hydroxy-2-fluoro-benzoic acid which was converted to benzyl 2-fluoro-4-hydroxybenzoate in a fashion analogous to that described in Example 23) was used as starting material in place of benzyl 2-chloro-4-hydroxy-benzoate.

NMR ($CDCl_3$): δ 0.91 (t, 3H), 0.97 (t, 3H), 1.02 (t, 3H), 1.30 (m, 2H), 1.7-2.1 (m, 6H), 2.32 (s, 3H), 4.83 (q, 1H), 5.70 (s, 1H), 6.9-7.3 (m, 6H), 7.94 (t, 1H)

EXAMPLE 36

(4S)-3,3-Diethyl-1-[(R)-α-n-propyl-(4-ethoxy)benzyl-aminocarbonyl]-4-[(4-carboxymethyl)phenoxy] azetidin-2-one

Step A: Preparation of (R)-α-allyl-(4-ethoxyphenyl)-methyl acetic acid, (R)-(+)-α-methylbenzyl-amine salt

A solution of 4-ethoxyphenylacetic acid (9.4 gm) in THF (50 ml) was cooled in a dry-ice bath under a nitrogen atmosphere and 110 ml of a 1M solution of lithium bis(trimethylsilyl)amide in THF was added dropwise. After 10 min the cooling bath was removed and and the solution was allowed to warm up. After an additional 30 min the flask was chilled in an ice-bath and allyl bromide (5.1 ml) was added. The reaction mixture was allowed to rise to room temperature over 1 hr and then was poured into aq. HCl/ice. This was extracted with Et_2O and the organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue so obtained was diluted with isopropanol (40 ml) and (R)-(+)-α-methylbenzylamine (3.5 gm) was added. A solid formed which was filtered off, and washed with cold isopropanol to give 4.08 gm of crude product. This solid was recrystallized twice from isopropanol to give 2.23 gm of the title compound as a white solid. $[\alpha]_D$ -20.42.

Step B: Preparation of (R)-α-allyl-(4-ethoxy)benzyl-isocyanate

2.2 gm of the material prepared in Step A above was acidified with 1.2N HCl in the presence

EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue so obtained was dissolved in acetone (12 ml) and added to a solution of NaN_3 (0.5 gm) in H_2O (9 ml), while maintaining the temperature below 5°C. After stirring for 0.5 hr, the solution was partitioned between H_2O and $CHCl_3$ and the organic layer was washed successively with H_2O and brine, and then dried over Na_2SO_4, filtered and concentrated to approximately 20 ml. This solution was heated on an oil bath at 60°C for 1 hr and then evaporated to dryness to give 1.4 gm of the title compound which was sufficiently pure for the next step.

Step C: Preparation of (4S)-3,3-diethyl-1-[(R)-α-allyl-(4-ethoxy)benzylaminocarbonyl]-4-[(4-benzyloxycarbonylmethyl)phenoxy]-azetidin-2-one

To a solution of the material prepared in Example 27 (0.5 gm) in CH_2Cl_2 (1 ml), 0.25 ml of Et_3N was added followed by 0.35 gm of the material prepared in Step B above and a trace of 4-dimethylaminopyridine. This solution was heated at 40°C for 3 days and the mixture was then diluted with CH_2Cl_2, washed successively with 1.2N HCl and brine, and then dried over Na_2SO_4, filtered and evaporated to dryness. The residue so obtained was purified by flash chromatography (silica gel, 10% to 30% EtOAc in hexane) to give 0.395 gm of the title compound.

Step D: Preparation of (4S)-3,3-diethyl-1-[(R)-α-n-propyl-(4-ethoxy)benzylaminocarbonyl]-4-[(4-carboxymethyl)-phenoxy]azetidin-2-one

To a solution of 0.395 gm of the the material prepared in Step C above in EtOH (4 ml) was added 5% Pd/C (50 mg) and the mixture was hydrogenated in a Parr apparatus for 5 hr. The catalyst was filtered off and washed with EtOAc. The filtrate was evaporated to dryness and the residue was purified by flash chromatography (silica gel, 30% to 40% EtOAc in hexane containing 0.5% HOAc) to give 0.298 gm of the title compound.

NMR (CDCl3): δ 0.91 (t, 3H), 0.95 (t, 3H), 1.08 (t, 3H), 1.30 (m, 2H), 1.41 (t, 3H), 1.7-2.1 (m, 6H), 3.61 (s, 2H), 4.04 (q, 2H), 4.82 (q, 1H), 5.58 (s, 1H), 6.8-7.3 (m, 9H)

EXAMPLE 37

(4S)-3,3-Diethyl-1-[(R)-α-n-propyl-(4-methyl)benzyl-aminocarbonyl]-4-[(4-carboxymethyl-3-chloro)phenoxy] azetidin-2-one

0.2 gm of material prepared in Example 34 was dissolved in CH_2Cl_2 (2 ml) and DMF (3 drops) and oxalyl chloride (0.06 ml) was added. Gas evolution occurred and after 30 min the solution was concentrated to dryness and the residue was diluted with Et_2O (3 ml). To this solution was added an ethereal solution of CH_2N_2. After 1 hr the reaction was added to a mixture of $AgNO_3$ (50 mg) and AgO (25 mg) in H_2O (5 ml)/THF (5 ml) at 70°C. After an additional 1 hr, the mixture was filtered through Celite and the fitrate was extracted with EtOAc. The organic layer was washed successively with H_2O and

brine and then dried over Na_2SO_4, filtered and evaporated to dryness. The residue so obtained was purified by flash chromatography (silica gel, using 30 - 40% EtOAc 1% acetic acid in hexane as eluant) to give 0.112 gm of the title compound.
NMR ($CDCl_3$): δ 0.90 (t, 3H), 0.94 (t, 3H), 1.06 (t, 3H), 1.32 (m, 2H), 1.6-2.1 (m, 6H), 2.32 (s, 3H), 3.76 (s, 2H), 4.85 (q, 1H), 5.55 (s, 1H), 6.93 (d, 1H), 7.1-7.4 (m, 6H), 7.98 (m, 1H)

EXAMPLE 38

(4S)-3,3-Diethyl-1-[(R)-α-n-propyl-(4-methyl)benzyl-aminocarbonyl]-4-[(4-carboxymethyl-3-fluoro)phenoxy] azetidin-2-one

The title compound was prepared essentially as described above for Example 37 except that the material prepared in Example 35 was used as starting material.
NMR ($CDCl_3$): δ 0.91 (t, 3H), 0.94 (t, 3H), 1.06 (t, 3H), 1.30 (m, 2H), 1.6-2.1 (m, 6H), 2.31 (s, 3H), 3.63 (s, 2H), 4.82 (q, 1H), 5.55 (s, 1H), 6.8-7.3 (m, 8H)

EXAMPLE 39

Starting with 3,3-diethyl-4-acetoxy-azetidin-2-one as prepared in Example 22, Step B (Scheme (d)) followed by displacement of the acetate with the appropriate phenol and acylation of the nitrogen with the corresponding chiral isocyanate as shown in Scheme (h) and Example 20, Steps C-E, the following compounds were prepared. The diastereomers obtained on acylation were separated by silica gel chromatography using 10-30% ethylacetate/hexane solvent mixtures.

(4S)-3,3-diethyl-1-[(R)-α-ethylbenzylaminocarbonyl]-4-[(4-carboxymethyl)phenoxy]azetidin-2-one.
NMR ($CDCl_3$): δ 0.9 (t,3H,J=7Hz), 0.94 (t,3H,J=7Hz), 1.07 (t,3H,J=7hz) 1.65 - 2.05 (m,6H), 3.58 (s,2H), 4.8 (q,1H, J=8Hz), 5.58 (s,1H), 7.0 (d, 1H, J= 8Hz), 7.1 - 7.45 (m,9H)

(4S)-3,3-diethyl-1-[(R)-α-n-propylbenzylamino-carbonyl]-4-[(4-carboxymethyl)phenoxy]azetidin-2-one.
NMR ($CDCl_3$): δ 0.91 (t,3H,J=7Hz), 0.94 (t,3H,J=7Hz), 1.07 (t,3H,J=7hz) 1.34 (m,2H), 1.65 -2.05 (m,6H), 3.57 (s,2H), 4.88 (q, 1H, J=7Hz), 5.58 (s,1H), 7.0 (d, 1H, J=7Hz) 7.1 - 7.5 (m, 9H)

(4S)-3,3-diethyl-1-[(R)-α-allyl-(4-methyl)benzyl-aminocarbonyl]-4-[(4-carboxymethyl)phenoxy]azetidin-2-one.
NMR ($CDCl_3$): δ 0.96 (t,3H,J=7Hz), 1.07 (t,3H,J=7Hz), 1.7 - 2.1 (m, 4H), 2.32 (s, 3H), 2.57 (t,2H, J=7Hz), 3.58 (s, 2H), 4.95 (q, 1H, J=7Hz), 5.14 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 7.03 (d, 1H, J=7Hz), 7.16 (s, 4H), 7.19 (s, 4H).

(4S)-3,3-diethyl-1-[(R)-α-allyl(3,4-methylenedioxy)-benzylaminocarbonyl]-4-[(4-carboxymethyl)phenoxy]-azetidin-2-one.
NMR ($CDCl_3$): δ 0.96 (t,3H,J=7Hz), 1.05 (t,3H,J=7Hz), 1.65 - 2.05 (m, 4H), 2.54 (t, 2H J=6Hz) 4.87 ((q, 1H, J=7Hz), 5.05 -5.2 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 5.94 (s, 2H), 6.76 (s, 3H), 6.98 41, 1H, J=7Hz), 7.2 (m,4H)).

(4S)-3,3-diethyl-1-[(R)-α-n-propyl(3,4-methylene-dioxy)-benzylaminocarbonyl]-4-[(4-carboxymethyl)-phenoxy]azetidin-2-one.
NMR ($CDCl_3$): δ 0.9 (t,3H,J=7Hz), 0.94 (t,3H,J=7Hz), 1.06 (t, 3H J=7Hz), 1.3 (m, 2H), 1.65 - 2.1 (m, 6H), 3.58(s, 2H), 4.76(q, 1H, J=7hz), 5.58(s, 1H), 5.92 (s,2H), 6.15 (s, 3H) 6.88 (d, 1H, J=7Hz), 7.2 (m, 4H).

(4S)-3,3-diethyl-1-[(R)-α-n-propyl(4-methyl)-benzylaminocarbonyl]-4-[(4-carboxy)phenoxy]azetidin-2-one.
NMR ($CDCl_3$): δ 0.91 (t,3H,J=7Hz), 0.98 (t,3H,J=7Hz), 1.07 (t, 3H, J=7Hz) 1.32 (m, 2H), 1.65 - 2.1 (m, 6H), 2.33(s, 3H), 4.83(q, 1H, J=7hz), 5.71(s, 1H), 6.93 (d, 1H, J=7Hz), 7.16 (s, 4H), 7.25 (d,2H,J=8Hz), 8.04 (d, 2H, J=8Hz).

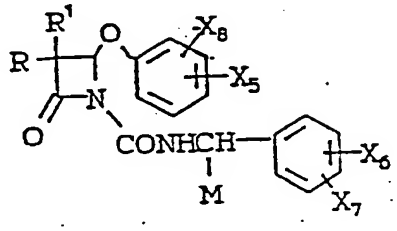
(4S)-3,3-diethyl-1-[(R)-α-n-propyl(4-methyl)-benzyl-aminocarbonyl]-4-[(4-carboxymethyl)phenoxy]azetidin-2-one.

NMR ($CDCl_3$): δ 0.9 (t,3H,J=7Hz), 0.93 (t,3H,J=7Hz), 1.07 (t, 3H, J=7Hz) 1.28 (m, 2H), 1.7 - 2.1 (m, 6H), 2.33(s, 2H), 3.6 (s,2H), 4.81 (q, 1H, J=7hz), 5.56 (s, 1H), 6.93 (d, 1H, J=7Hz), 7.15 (s, 4H), 7.2 (s, 4H).

(4S)-3,3-diethyl-1-[(R)-α-n-propyl(4-methoxy-3-methyl)-benzylaminocarbonyl]-4-[(4-carboxymethyl)-phenoxy]azetidin-2-one.
NMR ($CDCL_3$):

WHAT IS CLAIMED IS:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof for use in treating leukemia



(I)

wherein:

R is C_{1-6} alkyl;

R^1 is C_{1-6} alkyl or C_{1-6} alkoxy-C_{1-6} alkyl;

M is

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) hydroxy C_{1-6} alkyl,
(4) halo C_{1-6} alkyl,
(5) C_{2-6} alkenyl, or
(6) C_{1-6} alkoxy-C_{1-6} alkyl;

X_5 is

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo-C_{1-6} alkyl,
(4) C_{2-6} alkenyl,
(5) C_{2-6} alkynyl,
(6) carboxy,
(7) carboxy-C_{1-6} alkyl,

(8) carboxy-C_{1-6} alkylcarbonyl,
(9) carboxy-C_{1-6} alkylcarbonylamino,
(10) carboxy-C_{2-6} alkenyl,
(11) hydroxy-C_{1-6} alkyl,
(12) C_{1-6} alkylcarbonyl,
(13) C_{1-6} alkylcarbonylamino, or
(14) hydroxymethylcarbonyl C_{1-6} alkyl; and

X_6 and X_7 are each independently
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo,
(4) carboxy,
(5) C_{1-6} alkoxy,
(6) phenyl,
(7) C_{1-6} alkylcarbonyl;
(8) di-(C_{1-6}alkyl)amino,
(9) phenoxy, or

X_6 and X_7 are joined together to form the group 3,4-methylenedioxy or together with the atoms to which they are attached form furan or thiophene; and

X_8 is
(a) hydrogen,
(b) C_{1-6} alkyl,
(c) halo,
(d) C_{1-6} alkoxy, or
(e) hydroxy.

2. A use according to Claim 1 wherein
R is C_{1-6} alkyl;
R^1 is C_{1-6} alkyl or C_{1-6} alkoxy-C_{1-6} alkyl;
M is
(1) hydrogen,

(2) C_{1-6} alkyl,
(3) C_{2-6} alkenyl, or
(4) C_{1-6} alkoxy-C_{1-6} alkyl;

X_5 is
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo-C_{1-6} alkyl,
(4) C_{2-6} alkenyl,
(5) C_{2-6} alkynyl,
(6) carboxy,
(7) carboxy-C_{1-6} alkyl,
(8) carboxy-C_{1-6} alkylcarbonyl,
(9) carboxy-C_{1-6} alkylcarbonylamino,
(10) carboxy-C_{2-6} alkenyl,
(11) hydroxy-C_{1-6} alkyl,
(12) C_{1-6} alkylcarbonyl, or
(13) C_{1-6} alkylcarbonylamino,

X_6 is
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo,
(4) carboxy,
(5) C_{1-6} alkoxy,
(6) phenyl,
(7) C_{1-6} alkylcarbonyl,
(8) di-(C_{1-6}alkyl)amino,
(9) phenoxy, and

X_7 is hydrogen, or

X_6 and X_7 are joined together to form the group 3,4-methylenedioxy or together with the atoms to which they are attached form furan or thiophene; and

X_8 is hydrogen, C_{1-6}alkyl, fluoro or chloro.

3. A use according to Claim 2 wherein X_8 is hydrogen,
X_5 is
(1) carboxy, or
(2) carboxy-C_{1-6} alkyl.

4. A use according to Claim 3 wherein
M is
(1) C_{1-3} alkyl, or
(3) allyl; and
X_6 is
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) phenyl, or
X_6 and X_7 are joined together to form the group 3,4-methylenedioxy or together with the atoms to which they are attached form furan.

5. A use according to Claim 4 wherein:
R is methyl, ethyl or propyl; and
R^1 is methyl, ethyl or propyl.

6. A compound for use in treating leukemia which compound is selected from:

(a) (4S)-3,3-diethyl-1-((R)-α-ethyl-benzyl-amino-carbonyl)-4-(4-carboxymethyl)-phenoxyazetidin-2-one;
(b) (4S)-3,3-diethyl-1-((R)-α-n-propyl-benzyl-amino-carbonyl)-4-(4-carboxymethyl)-phenoxyazetidin-2-one;

(c) (4S)-3,3-diethyl-1-((R)-α-allyl-(4-methyl)benzyl amino-carbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one;
(d) (4S)-3,3-diethyl-1-((R)-α-allyl-(3,4-methylene-dioxy)-benzyl-aminocarbonyl)-4-(4-carboxymethyl)-phenoxyazetidin-2-one;
(e) (4S)-3,3-diethyl-1-((R)-α-n-propyl-(3,4-methylenedioxy)-benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one;
(f) (4S)-3,3-diethyl-1-((R)-α-n-propyl-(4-methyl)-benzylamino-carbonyl)-4-(4-carboxy)phenoxyazetidin-2-one;
(g) (4S)-3,3-diethyl-1-((R)-α-n-propyl-(4-methyl)-benzylamino-carbonyl)-4-(4-carboxymethyl)-phenoxy azetidin-2-one.
(h) (4S)-3,3-Diethyl-1-[(R)-α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4- carboxy-3-chloro)phenoxy]azetidin-2-one;
(i) (4S)-3,3-Diethyl-1-[(R)-α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4- carboxy-3-fluoro)phenoxy]azetidin-2-one;
(j) (4S)-3,3-Diethyl-1-[(R)- α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4- carboxy-3-methyl)-phenoxy]azetidin-2-one;
(k) (4S)-3,3-Diethyl-1-[(R)- α-n-propyl-(4-ethoxy)benzylaminocarbonyl]-4-[(4- carboxymethyl) phenoxy]azetidin-2-one;
(l) (4S)-3,3-Diethyl-1-[(R)- α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4- carboxymethyl-3-chloro)phenoxy]azetidin-2-one; and
(m) (4S)-3,3-Diethyl-1-[(R)- α-n-propyl-(4-methyl)benzylaminocarbonyl]-4-[(4- carboxymethyl-3-fluoro)phenoxy]azetidin-2-one;
and pharmaceutically acceptable salts thereof.

7. The compound (4S)-3,3-diethyl-1-((R)-α-n-propyl-(4-methyl)-benzylamino-carbonyl)-4-(4-carboxymethyl)-phenoxy azetidin-2-one for use in treating leukaemia.

8. A compound selected from:

(4S)-3,3-diethyl-1-((R)-α-n-propyl-(4-methyl)-benzylamino-carbonyl)-4-(4-carboxy)phenoxy-azetidin-2-one; or
(4S)-3,3-diethyl-1-[[(R)- 1-(benzofuran-5-yl)butyl-amino]carbonyl]-4-[(4-carboxymethyl)-phenoxy]azetidin-2-one
for use in treating leukaemia.

9. A pharmaceutical composition for treating leukemia comprising:
a pharmaceutical carrier, a therapeutically effective amount of compound selected from the group consisting of epsilon-aminocaproic acid, heparin, trasylol, prednisolone, cytosine arabinoside, b-mercaptopurine, cytarabine, an anthracycline and a vitamin A derivative; and a therapeutically effective amount of compound according any of Claims 1-8.

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

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Relevant Technical fields

(i) UK Cl (Edition L) C2C CKM; A5B

(ii) Int Cl (Edition 5) C07D, A61K

Search Examiner
P N DAVEY

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASES: CAS ONLINE

Date of Search
26 JULY 1993

Documents considered relevant following a search in respect of claims 1-9

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
P,X	EP 0481671 A1 (MERCK) 22 April 1992, see formula A and page 30 line 19	1, 9 at least
X	EP 0337549 A1 (MERCK) see for example formula A	1 at least

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

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